CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-323/S-003 & 21-365/S-004

Trade Name:	Lexapro Tablets/Oral Solution
Generic Name:	escitalopram oxalate
Sponsor:	Forest Laboratories, Inc.
Approval Date:	December 18, 2003
Indications:	For the treatment of generalized anxiety disorder.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-003 & 21-365/S-004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-003 & 21-365/S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-323/S-003/S-007
NDA 21-365/S-001/S-004

Forest Laboratories, Inc.
Attention: Andrew Friedman, R.Ph.
Manager, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Dear Mr. Friedman:

Please refer to your supplemental new drug applications dated November 26, 2002 (NDA 21-323/S-003 & 21-365/S-004), and February 6, 2003 (NDA 21-323/S-007 & 21-365/S-001), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) Tablets (NDA 21-323) and Lexapro (escitalopram oxalate) Oral Solution (NDA 21-365).

We acknowledge receipt of your submissions dated October 20, October 27, December 4, and December 11, 2003.

Your submission of October 20, 2003, constituted a complete response to our September 26, 2003 action letter for supplemental applications 21-323/S-003 & 21-365/S-004, and your submission of December 11, 2003, constituted a complete response to our November 25, 2003 action letter for supplemental applications 21-323/S-007 & 21-365/S-001.

These supplements provide for the following revisions to labeling:

Under supplemental applications 21-323/S-007 & 21-365/S-001: efficacy study reports from Studies 99001 & 99003 as additional trials supporting the efficacy of escitalopram in the treatment of major depressive disorder.

Under supplemental applications 21-323/S-003 & 21-365/S-004: treatment of generalized anxiety disorder.

We have completed the review of these applications, 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 enclosed labeling text. Accordingly, these applications are approved effective on the date of this letter.

We note your agreement to the attached labeling in conference calls dated December 11, and 16, 2003, between the Agency and representatives from Forest.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements 21-323/S-003/S-007 & NDA 21-365/S-001/S-004." Approval of these submissions by FDA is not required before the labeling is used.

Additionally, we are requesting that you submit a "Prior Approval" supplemental new drug application to incorporate a new subsection under **ADVERSE REACTIONS** entitled **Events Reported Subsequent to the Marketing of Escitalopram.** This section should include all of the adverse events reported since marketing of escitalopram and not reported during the premarketing of escitalopram and the postmarketing of citalopram, i.e., these events would be postmarketing adverse events specific to escitalopram. This supplement should also contain the data to support your proposed additions to product labeling.

This supplement should be submitted within 60 days of this letter.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

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

Attachment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
12/18/03 09:31:43 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-003 & 21-365/S-004

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-323/S-003 & NDA 21-365/S-004

Forest Laboratories, Inc.
Attention: Andrew Friedman, R.Ph.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Mr. Friedman:

Please refer to your supplemental new drug applications dated November 26, 2002, and May 21, 2003, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro® (escitalopram oxalate) Tablets and Oral Solution, respectively.

We acknowledge receipt of your amendments dated January 7 and March 12, 2003 (NDA 21-323/S-003).

These supplemental new drug applications provide for the use of Lexapro® Tablets and Oral Solution for the treatment of generalized anxiety disorder.

We have completed the review of these applications, as submitted with the draft labeling, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

Chemistry Issues

1. Please describe in detail the following: the encapsulated Lexapro™ (escitalopram oxalate) Tablet formulation 10 mg, 20 mg, the encapsulated Celexa™ (citalopram HBr) 20 mg and 40 mg, the placebo capsule formulation, used in the efficacy trials for GAD. Please include a detailed description of the capsule shell (i.e., size, color, manufacturer, and acceptance testing, including methods and specifications) and a detailed description of the materials used to fill the clinical capsule formulation.

2. Please provide dissolution results (i.e., dissolution plots and f2 calculations) demonstrating that the encapsulated Lexapro™ (escitalopram oxalate) Tablet formulation 10 mg, 20 mg and the encapsulated Celexa™ (citalopram HBr) Tablet formulation 20 mg, 40 mg release drug in a manner which is identical to the approved drug products.

Labeling

Accompanying this letter as an attachment is our proposal for the labeling for Lexapro® Tablets and Oral Solution for the generalized anxiety disorder indication. Please submit revised draft labeling, including the latest revisions for the oral solution (NDA 21-365), and the recommended revisions for the generalized anxiety disorder indication in the enclosed labeling (text for the package insert for the tablet formulation). Explanations for our proposed changes are also provided.

Safety Update

Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for Lexapro® for the generalized anxiety disorder indication.

Regulatory Status Update

Please provide any new information on the worldwide regulatory status of Lexapro® for generalized anxiety disorder, including the status of all actions either taken or pending before foreign regulatory authorities.

World Literature Update

Prior to approval, we will require an updated report on the world archival literature pertaining to the safety of this product for this indication.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you should have any questions, please call Ms. Anne Marie H. Weikel, R.Ph., Senior Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

Enclosure

27 page(s) of draft labeling has been removed from this portion of the review.

Approvable Letter

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/s/

Russell Katz
9/26/03 02:54:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-003 & 21-365/S-004

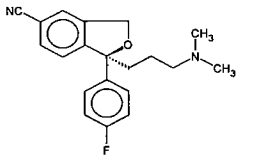
LABELING

LEXAPRO™
(escitalopram oxalate)
TABLETS/ORAL SOLUTION

Rx Only

DESCRIPTION

LEXAPRO™ (escitalopram oxalate) is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3-(dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula:



• $C_2H_2O_4$

The molecular formula is $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ and the molecular weight is 414.40.

Escitalopram oxalate occurs as a fine white to slightly yellow powder and is freely soluble in methanol and dimethyl sulfoxide (DMSO), soluble in isotonic saline solution, sparingly soluble in water and ethanol, slightly soluble in ethyl acetate, and insoluble in heptane.

LEXAPRO (escitalopram oxalate) is available as tablets or as an oral solution.

LEXAPRO tablets are film coated, round tablets containing escitalopram oxalate in strengths equivalent to 5 mg, 10 mg and 20 mg escitalopram base. The 10 and 20 mg tablets are scored. The tablets also contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hydroxypropyl methyl cellulose, titanium dioxide, and polyethylene glycol.

LEXAPRO oral solution contains escitalopram oxalate equivalent to 1 mg/mL escitalopram base. It also contains the following inactive ingredients: sorbitol, purified water, citric acid, sodium citrate, malic acid, glycerin, propylene glycol, methylparaben, propylparaben, and natural peppermint flavor.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100 fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta-adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. Escitalopram also does not bind to or has low affinity for various ion channels including Na^+, K^+, Cl^- and Ca^{++} channels. Antagonism of muscarinic, histaminergic and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular side effects of other psychotropic drugs.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

Absorption and Distribution

Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food.

The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12 L/kg. Data specific on escitalopram are unavailable.

The binding of escitalopram to human plasma proteins is approximately 56%.

Metabolism and Elimination

Following oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.

Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the

concentration of the escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta- adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na^+, K^+, Cl^- and Ca^{++} channels.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Population Subgroups

Age - Escitalopram pharmacokinetics in subjects $\geq$ 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients (see Dosage and Administration).

Gender - In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max} and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Reduced hepatic function - Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is the recommended dose of escitalopram for most hepatically impaired patients (see Dosage and Administration).

Reduced renal function - In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on CYP3A4, -1A2, -2C9, -2C19, and -2E1. Based on *in vitro* data, escitalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. While *in vivo* data to address this question are limited, results from drug interaction studies suggest that escitalopram, at a dose of 20 mg, has no 3A4 inhibitory effect and a modest 2D6 inhibitory effect. See Drug Interactions under Precautions for more detailed information on available drug interaction data.

Clinical Efficacy Trials

Major Depressive Disorder

The efficacy of LEXAPRO as a treatment for major depressive disorder was established in three, 8-week, placebo-controlled studies conducted in outpatients between 18 and 65 years of age who met DSM-IV criteria for major depressive disorder. The primary outcome in all three studies was change from baseline to endpoint in the Montgomery Asberg Depression Rating Scale (MADRS).

A fixed dose study compared 10 mg/day LEXAPRO and 20 mg/day LEXAPRO to placebo and 40 mg/day citalopram. The 10 mg/day and 20 mg/day LEXAPRO treatment groups showed significantly greater mean improvement compared to placebo on the MADRS. The 10 mg and 20 mg LEXAPRO groups were similar on this outcome measure.

In a second, fixed dose study of 10 mg/day LEXAPRO and placebo, the 10 mg/day LEXAPRO treatment group showed significantly greater mean improvement compared to placebo on the MADRS.

In a flexible dose study, comparing LEXAPRO, titrated between 10 and 20 mg/day, to placebo and citalopram, titrated between 20 and 40 mg/day, the LEXAPRO treatment group showed significantly greater mean improvement compared to placebo on the MADRS.

Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

In a longer-term trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week open label treatment phase with LEXAPRO 10 or 20 mg/day, were randomized to continuation of LEXAPRO at their same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open label phase was defined by having a decrease of the MADRS total score to ≤ 12. Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22, or discontinuation due to insufficient clinical response. Patients receiving continued LEXAPRO experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo.

Generalized Anxiety Disorder

The efficacy of LEXAPRO in the treatment of Generalized Anxiety Disorder (GAD) was demonstrated in three 8-week, multicenter, flexible dose, placebo-controlled studies that compared LEXAPRO 10-20 mg/day to placebo in outpatients between 18 and 80 years of age who met DSM-IV criteria for GAD. In all three studies, LEXAPRO showed significantly greater mean improvement compared to placebo on the Hamilton Anxiety Scale (HAM-A) .

There were too few patients in differing ethnic and age groups to adequately assess whether or not LEXAPRO has differential effects in these groups. There was no difference in response to LEXAPRO between men and women.

INDICATIONS AND USAGE

Major Depressive Disorder
LEXAPRO (escitalopram) is indicated for the treatment of major depressive disorder.

The efficacy of LEXAPRO in the treatment of major depressive disorder was established in three, 8-week, placebo-controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-IV category of major depressive disorder (see 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 efficacy of LEXAPRO in hospitalized patients with major depressive disorders has not been adequately studied.

The efficacy of LEXAPRO in maintaining a response, in patients with major depressive disorder who responded during an 8-week acute treatment phase while taking LEXAPRO and were then observed for relapse during a period of up to 36 weeks, was demonstrated in a placebo-controlled trial (see Clinical Efficacy Trials, under Clinical Pharmacology). Nevertheless, the physician who elects to use LEXAPRO for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

Generalized Anxiety Disorder
LEXAPRO is indicated for the treatment of Generalized Anxiety Disorder (GAD).

The efficacy of LEXAPRO was established in three 8-week placebo-controlled trials in patients with GAD (see Clinical Pharmacology).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

The efficacy of LEXAPRO in the long term treatment of GAD, that is, for more than 8 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use LEXAPRO for extended periods should periodically re-evaluate the long term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see Warnings).

LEXAPRO is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in LEXAPRO.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), 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. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that LEXAPRO should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping LEXAPRO before starting a MAOI.

Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid an antibiotic which is a reversible non-selective MAOI.

PRECAUTIONS

General

Discontinuation of Treatment with LEXAPRO

During marketing of Lexapro and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with LEXAPRO. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of LEXAPRO with NSAIDS, aspirin, or other drugs that affect coagulation.

Hyponatremia

One case of hyponatremia has been reported in association with LEXAPRO treatment. Several cases of hyponatremia or SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with racemic citalopram. All patients with these events have recovered with discontinuation of escitalopram or citalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder.

Activation of Mania/Hypomania

In placebo-controlled trials of LEXAPRO in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with LEXAPRO and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with LEXAPRO treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, LEXAPRO should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of racemic citalopram have been observed in animal studies, LEXAPRO has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of LEXAPRO, cases of convulsion have been reported in association with LEXAPRO treatment. Like other drugs effective in the treatment of major depressive disorder, LEXAPRO should be introduced with care in patients with a history of seizure disorder.

Suicide

The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. As with all drugs effective in the treatment of major depressive disorder,

prescriptions for LEXAPRO should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Interference with Cognitive and Motor Performance

In a study in normal volunteers, LEXAPRO 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that LEXAPRO therapy does not affect their ability to engage in such activities.

Use in Patients with Concomitant Illness

Clinical experience with LEXAPRO in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using LEXAPRO in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

LEXAPRO has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of LEXAPRO in hepatically impaired patients is 10 mg/day (see Dosage and Administration).

Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with LEXAPRO, however, it should be used with caution in such patients (see Dosage and Administration).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe LEXAPRO.

In a study in normal volunteers, LEXAPRO 10 mg/day did not impair psychomotor performance. The effect of LEXAPRO on psychomotor coordination, judgment, or thinking has not been systematically examined in controlled studies. Because psychoactive drugs may impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that LEXAPRO therapy does not affect their ability to engage in such activities.

Patients should be told that, although LEXAPRO has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of LEXAPRO and alcohol in depressed patients is not advised.

Patients should be made aware that escitalopram is the active isomer of Celexa (citalopram hydrobromide) and that the two medications should not be taken concomitantly.

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.

Patients should be cautioned about the concomitant use of LEXAPRO and NSAIDS, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

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

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

While patients may notice improvement with LEXAPRO therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Laboratory Tests

There are no specific laboratory tests recommended.

Concomitant Administration with Racemic Citalopram

Citalopram – Since escitalopram is the active isomer of racemic citalopram (Celexa), the two agents should not be coadministered.

Drug Interactions

CNS Drugs - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Alcohol - Although LEXAPRO did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking LEXAPRO is not recommended.

Monoamine Oxidase Inhibitors (MAOIs) - See Contraindications and Warnings.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with LEXAPRO.

Cimetidine - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.

Digoxin - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium - Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when LEXAPRO and lithium are coadministered.

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, escitalopram) is clinically warranted, appropriate observation of the patient is advised.

Theophylline – Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Warfarin - Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

Carbamazepine - Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered.

Triazolam – Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

Ketoconazole – Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

Ritonavir – Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram.

CYP3A4 and -2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

Drugs Metabolized by Cytochrome P4502D6 - *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in Cmax and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

Metoprolol - Administration of 20 mg/day LEXAPRO for 21 days in healthy volunteers resulted in a 50% increase in Cmax and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of LEXAPRO and metoprolol had no clinically significant effects on blood pressure or heart rate.

Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of ECT and escitalopram.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation.

It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Impairment of Fertility

When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day.

Pregnancy

Pregnancy Category C

In a rat embyro/fetal development study, oral administration of escitalopram (56, 112 or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis).

When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was seen at 24 mg/kg/day. The no effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis.

In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased BW gain). The developmental no effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic

citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥24 mg/kg/day. A no effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects

Neonates exposed to LEXAPRO and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

When treating a pregnant woman with LEXAPRO during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

Labor and Delivery

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

Nursing Mothers

Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breast feeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow up information was available. The decision whether to continue or discontinue either nursing or LEXAPRO therapy should take into account the risks of citalopram exposure for the infant and the benefits of LEXAPRO treatment for the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of LEXAPRO in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of LEXAPRO between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of LEXAPRO cannot be ruled out.

In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged (see Clinical Pharmacology). 10 mg/day is the recommended dose for elderly patients (see Dosage and Administration).

Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. 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 again, greater sensitivity of some elderly individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse event information for LEXAPRO was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for LEXAPRO in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using 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 smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.

The stated frequencies of adverse events 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.

Adverse Events Associated with Discontinuation of Treatment

Major Depressive Disorder

Among the 715 depressed patients who received LEXAPRO in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2 % of 592 patients receiving placebo. In two fixed dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day LEXAPRO was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day LEXAPRO was 10% which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day LEXAPRO (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with LEXAPRO, and for which the rate was at least twice the placebo rate, were nausea (2%) and ejaculation disorder (2% of male patients).

Generalized Anxiety Disorder

Among the 429 GAD patients who received LEXAPRO 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4 % of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with LEXAPRO, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%).

Incidence of Adverse Events in Placebo-Controlled Clinical Trials

Major Depressive Disorder

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment emergent adverse events that occurred among 715 depressed patients who received LEXAPRO at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with LEXAPRO and for which the incidence in patients treated with LEXAPRO was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The most commonly observed adverse events in LEXAPRO patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see TABLE 1).

TABLE 1
Treatment-Emergent Adverse Events:
Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder *

	(Percentage of Patients Reporting Event)	
Body System / Adverse Event	**LEXAPRO (N=715)**	**Placebo (N=592)**
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

*Events reported by at least 2% of patients treated with LEXAPRO are reported, except for the following events which had an incidence on placebo ≥ LEXAPRO: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety.

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=225 LEXAPRO ; N=188 placebo).
[3]Denominator used was for females only (N=490 LEXAPRO ; N=404 placebo).

Generalized Anxiety Disorder

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment emergent adverse events that occurred among 429 GAD patients who received LEXAPRO 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with LEXAPRO and for which the incidence in patients treated with LEXAPRO was greater than the incidence in placebo-treated patients.

The most commonly observed adverse events in LEXAPRO patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 2).

TABLE 2
Treatment-Emergent Adverse Events:
Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder*

Body System / Adverse Event	(Percentage of Patients Reporting Event) LEXAPRO (N=429)	Placebo (N=427)
Autonomic Nervous System Disorders		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Yawning	2%	1%
Urogenital		
Ejaculation Disorder[1,2]	14%	2%
Anorgasmia[3]	6%	<1%
Menstrual Disorder	2%	1%

*Events reported by at least 2% of patients treated with LEXAPRO are reported, except for the following events which had an incidence on placebo ≥ LEXAPRO: inflicted injury, ,dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis.
[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=182 LEXAPRO; N=195 placebo).

[3]Denominator used was for females only (N=247 LEXAPRO; N=232 placebo).

Dose Dependency of Adverse Events

The potential dose dependency of common adverse events (defined as an incidence rate of ∃ 5% in either the 10 mg or 20 mg LEXAPRO groups) was examined on the basis of the combined incidence of adverse events in two fixed dose trials. The overall incidence rates of adverse events in 10 mg LEXAPRO treated patients (66%) was similar to that of the placebo treated patients (61%), while the incidence rate in 20 mg/day LEXAPRO treated patients was greater (86%). Table 2 shows common adverse events that occurred in the 20 mg/day LEXAPRO group with an incidence that was approximately twice that of the 10 mg/day LEXAPRO group and approximately twice that of the placebo group.

TABLE 3
Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo, 10 mg/day LEXAPRO, or 20 mg/day LEXAPRO

Adverse Event	Placebo (N=311)	10 mg/day LEXAPRO (N=310)	20 mg/day LEXAPRO (N=125)
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

*Adverse events with an incidence rate of at least 5% in either of the LEXAPRO groups and with an incidence rate in the 20 mg/day LEXAPRO group that was approximately twice that of the 10 mg/day LEXAPRO group and the placebo group.

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.

Table 4 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo controlled trials.

TABLE 4
Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials

Adverse Event	LEXAPRO™	Placebo
	In Males Only	
	(N= 407)	(N= 383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Decreased Libido	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N= 737)	(N= 636)
Decreased Libido	3%	1%
Anorgasmia	3%	<1%

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

Vital Sign Changes

LEXAPRO and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with LEXAPRO treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving LEXAPRO indicated that LEXAPRO treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with LEXAPRO in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes

LEXAPRO and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with LEXAPRO treatment.

ECG Changes

Electrocardiograms from LEXAPRO (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for LEXAPRO and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for LEXAPRO and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither LEXAPRO nor racemic citalopram were associated with the development of clinically significant ECG abnormalities.

Other Events Observed During the Premarketing Evaluation of LEXAPRO

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with LEXAPRO for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 1& 2, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with LEXAPRO, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients.

Cardiovascular – *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein.

Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased.

Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult.

General – *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent*: edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall.

Hemic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical.

Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia.

Musculoskeletal System Disorders – *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness.

Psychiatric Disorders – *Frequent*: appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency.

Reproductive Disorders/Female* - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses.

*% based on female subjects only: N= 905

Respiratory System Disorders - *Frequent*: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis.

Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule.

Special Senses - *Frequent:* vision blurred, tinnitus. *Infrequent*: taste alteration, ear ache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste.

Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent*: urinary urgency, kidney stone, dysuria, blood in urine.

Events Reported Subsequent to the Marketing of Racemic Citalopram

Although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment and were not observed during the premarketing evaluation of ~~escitalopram or~~ citalopram: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

LEXAPRO is not a controlled substance.

Physical and Psychological Dependence

Animal studies suggest that the abuse liability of racemic citalopram is low. LEXAPRO has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with LEXAPRO did not reveal any drug seeking behavior. However, 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 LEXAPRO patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE

Human Experience

There have been five reports of LEXAPRO overdose involving doses of up to 600 mg. All five patients recovered and no symptoms associated with the overdoses were reported. In clinical trials of racemic citalopram, there were no reports of fatal citalopram overdose involving overdoses of up to 2000 mg. During the postmarketing evaluation of citalopram, like other SSRIs, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely reported.

Postmarketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920 mg and 2800 mg), as well as non-fatal overdoses of up to 6000 mg. Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, sinus tachycardia, and convulsions. In more rare cases, observed symptoms included amnesia, confusion, coma, hyperventilation,

cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of Torsades de pointes).

Management of Overdose

Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for LEXAPRO.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Initial Treatment

The recommended dose of LEXAPRO is 10 mg once daily. A fixed dose trial of LEXAPRO demonstrated the effectiveness of both 10 mg and 20 mg of LEXAPRO, but failed to demonstrate a greater benefit of 20 mg over 10 mg (see Clinical Efficacy Trials under Clinical Pharmacology). If the dose is increased to 20 mg, this should occur after a minimum of one week.

LEXAPRO should be administered once daily, in the morning or evening, with or without food.

Special Populations

10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment.

No dosage adjustment is necessary for patients with mild or moderate renal impairment. LEXAPRO should be used with caution in patients with severe renal impairment.

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to LEXAPRO and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with LEXAPRO during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering LEXAPRO in the third trimester.

Maintenance Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of continuing LEXAPRO 10 or 20 mg/day for periods of up to 36 weeks in patients with major depressive disorder who responded while taking LEXAPRO during an 8-week acute treatment phase demonstrated a benefit of such maintenance treatment (see Clinical Efficacy Trials, under Clinical Pharmacology). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Generalized Anxiety Disorder

Initial Treatment
The recommended starting dose of LEXAPRO is 10 mg once daily. If the dose is increased to 20 mg, this should occur after a minimum of one week.

LEXAPRO should be administered once daily, in the morning or evening, with or without food.

Maintenance Treatment
Generalized anxiety disorder is recognized as a chronic condition. The efficacy of LEXAPRO in the treatment of GAD beyond 8 weeks has not been systematically studied. The physician who elects to use LEXAPRO for extended periods should periodically reevaluate the long term usefulness of the drug for the individual patient.

Discontinuation of Treatment with LEXAPRO

Symptoms associated with discontinuation of LEXAPRO and other SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of LEXAPRO therapy. Similarly, at least 14 days should be allowed after stopping LEXAPRO before starting a MAOI (see Contraindications and Warnings).

HOW SUPPLIED

5 mg Tablets:

Bottle of 30	NDC # 0456-2005-30
Bottle of 100	NDC # 0456-2005-01
Bottle of 1000	NDC # 0456-2005-00
10 x 10 Unit Dose	NDC # 0456-2005-63

White to off-white, round, non-scored film coated. Imprint "FL" on one side of the tablet and "5" on the other side.

10 mg Tablets:

Bottle of 30	NDC # 0456-2010-30
Bottle of 100	NDC # 0456-2010-01
Bottle of 1000	NDC # 0456-2010-00
10 x 10 Unit Dose	NDC # 0456-2010-63

White to off-white, round, scored film coated. Imprint on scored side with "F" on the left side and "L" on the right side.
Imprint on the non-scored side with "10"

20 mg Tablets:

Bottle of 30	NDC # 0456-2020-30
Bottle of 100	NDC # 0456-2020-01
Bottle of 1000	NDC # 0456-2020-00
10 x 10 Unit Dose	NDC # 0456-2020-63

White to off-white, round, scored film coated. Imprint on scored side with "F" on the left side and "L" on the right side.
Imprint on the non-scored side with "20".

Oral Solution:
5 mg/5 mL, peppermint flavor - (240 mL) NDC # 0456-2101-08

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59-86°F).

ANIMAL TOXICOLOGY

Retinal Changes in Rats

Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with racemic citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day. Similar findings were not present in rats receiving 24 mg/kg/day of racemic citalopram for two years, in mice receiving up to 240 mg/kg/day of racemic citalopram for 18 months, or in dogs receiving up to 20 mg/kg/day of racemic citalopram for one year.

Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

Cardiovascular Changes in Dogs

In a one year toxicology study, 5 of 10 beagle dogs receiving oral racemic citalopram doses of 8 mg/kg/day died suddenly between weeks 17 and 31 following initiation of treatment. Sudden deaths were not observed in rats at doses of racemic citalopram up to 120 mg/kg/day, which produced plasma levels of citalopram and its metabolites demethylcitalopram and didemethylcitalopram (DDCT) similar to those observed in dogs at 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, racemic DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045 USA

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Rev. 12/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-003 & 21-365/S-004

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	21-323 SE1-003 (oral tablet formulation) 21-365 SE1-004 (oral solution formulation)
Sponsor:	Forest Laboratories, Inc.
Drug	
Established Name:	Escitalopram oxalate
Chemical Name:	(+)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
Code Name:	Lu 26-054
Formulation:	10 mg and 20 mg encapsulated tablets (also 20 and 40 mg citalopram encapsulated tablets and placebo were employed)
Indication:	Generalized Anxiety Disorder
Dates of Submission:	November 26, 2002
Materials Reviewed:	Three 8-Week Placebo Controlled, Multi-Center, Double-blind, Parallel group, Flexible dose (10 to 20 mg/day of escitalopram), clinical Trials (SCT-MD-05, SCT-MD-06, SCT-MD-07) on the Safety and Efficacy of Escitalopram in approximately 870 randomized adults with Generalized Anxiety disorder.
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	7/1/03

EXECUTIVE SUMMARY

Purpose of this review: This review and summary are to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-323 SE1-003. The summary provides a brief overview of the Clinical review of NDA 21-323 (refer to the review for more complete and detailed clinical information and clinical recommendations).

Summary: Escitalopram (SCT) is the S-enantiomer of citalopram, a selective serotonin reuptake inhibitor (SSRI). SCT was recently approved for the indication (MDD) under the brand name of Lexapro.™ Citalopram is currently marketed under the brand name of Celexa™ for Major Depressive Disorder (MDD). The sponsor is now seeking approval for the indication of Generalized Anxiety Disorder (GAD).

To support their proposed GAD claim, the sponsor describes three positive, multicenter, placebo controlled, double-blind depression trials (SCT-MD-05, -MD-06 and -MD-07). These studies employed a parallel group, flexible dose design (10-20 mg of SCT/day) of double-blind treatment given over an eight week period. A total of approximately 870 randomized Ss were included in the three studies. Subjects were required to meet DSM-IV criteria for GAD.

Safety results of the GAD trials and other completed or ongoing trials were similar to those described in previous Clinical reviews under this NDA. Based on the efficacy results, as described by the sponsor, each of the three positive studies showed significantly greater improvement on the primary efficacy variable, mean change from baseline to treatment endpoint (week eight) on the Hamilton Anxiety Rating scale score. Secondary efficacy results were generally consistent with a treatment effect of greater improvement of GAD in SCT treated patients compared to placebo.

One critical issue revealed by the Biometric Reviewer is that an unusually large proportion of study sites in Studies MD-05 and-06 showed results in the negative direction (i.e. numerically greater improvement in the placebo group compared to the SCT group on the primary efficacy variable). The study site with the greatest treatment group mean difference on the primary efficacy variable in each of the three trials was found to be in the positive direction (and the mean treatment group difference in each outlier site was greater than 2 standard deviations from mean treatment group difference for all sites, combined). The outlier site in two of the studies, Studies MD-05 and -06, had a mean treatment group difference that was large enough to skew the overall results in each respective trial, in the positive direction based on the following. The Biometric Reviewer reanalyzed the data of each of the three trials, excluding data from the outlier study site in each given trial (i.e. the site with the numerically greatest treatment group difference on the mean change from baseline to endpoint on the primary efficacy variable). This reanalysis revealed that Studies, MD-05 and -06 were no longer positive (no longer showed statistically significant results with $p=0.06$ and $p=0.15$, respectively), while Study MD-07 remained positive upon deleting the data from the outlier site ($p< 0.0001$). Therefore, DSI will be conducting an investigation of the two outliers sites in Studies, MD-05 and -06, as identified by the Biometric Reviewer. From a Clinical perspective, it is recommended that this supplemental NDA be given an approvable status. However, it is recommended that final approval not be considered if DSI reveals any remarkable findings or if the Biometric Reviewer cannot resolve the above biometric-related issues. If these outstanding issues can be resolved, then proposed labeling generally appears to be acceptable with some exceptions as described in this review.

Table of Contents

I. Introduction and Background.

This review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-323 SE1-011.

A. Indication and Proposed Direction of Use

The sponsor is proposing a new indication of Generalized Anxiety Disorder (GAD) for Lexapro™ (escitalopram). Escitalopram (SCT) is the S-enantiomer of citalopram (the racemate), a selective reuptake serotonin inhibitor (SSRI). Citalopram is currently marketed under the brand name of Celexa™ for Major Depressive disorder (MDD). SCT (Lexapro™) in both tablet (NDA 21-323) and oral solution (NDA21-365) formulations were recently approved for the MDD indication (dated 8/14/02).

Current approved Lexapro™ (Lex) labeling recommends a starting daily oral dose of 10 mg for MDD, but is also effective at a daily dose of 20 mg. However, this higher dose "failed to demonstrate a greater benefit" over 10 mg. The dose may be increased to 20 mg daily, after a minimum interval of one week at the lower dose. The dose may be administered with or without food, in the evening or in the morning.

The proposed direction for use of Lex for GAD is similar to that for MDD. However, regarding a dose increase the following statement is proposed by the sponsor: [redacted]

B. State of Armamentarium for Indication

Classes of drug products currently approved for treatment of GAD (or "nonpsychotic" GAD) include the following with some examples provided (administered orally unless otherwise specified):

- SSRIs: Paroxetine
- 1,4 Benzodiazepines: alprazolam (Xanax®)
- Serotonin$_{1A}$ agonist: Buspirone (Buspar®)
- Serotonin and norepinephrine reuptake inhibitors: Venlafaxine (Effexor®XR, the extended release formulation) which also is a weak inhibitor of dopamine reuptake).
- Phenothiazines: prochlorperazine (Compazine®) which is a phenothiazine derivative in which formulations for oral and intramuscular (i.m.) administration are approved for GAD, trifluperazine (Stellazine®) which is approved for both oral and i.m formulations.

Off-label use of a variety of SSRIs or other medications in other drug classes approved for MDD is common for the treatment of GAD. Some of these drugs are approved for other anxiety disorders, such as Social Anxiety Disorder. The off-label practice of treating GAD patients with adjunctive antidepressant treatment with an anxiolytic agent is fairly common, since patients with GAD frequently have concurrent MDD (or depressive symptoms). Less often, antipsychotic agents (not approved for "anxiety"), may be used off-label for GAD (at least for short-term, as an effort to ameliorate severe symptoms). GABA agonists (not approved for anxiety or GAD) are typically used off-label. Sedative hypnotic agents or drugs with sedative-like effects are used off-label for treating a common symptom of insomnia in GAD patients (e.g. some antipsychotic or antidepressant agents).

A variety of benzodiazepines and non-benzodiazepines believed to act on GABA receptors (such as hydroxycine HCl or Atarax®, Alprazolam or Xanax®, among others) are

approved for "anxiety" or "nonpsychotic anxiety" and are used off-label for GAD. A monamine oxidase inhibitor (Nardil®) is approved for "anxiety." Barbiturates, and opiod analgesics are among the oldest drugs approved for "anxiety" and are less commonly (i.e. rarely) used, primarily due to greater safety risks associated with these drugs.

C. Administrative History

The development of Lexapro™ for the GAD indication was conducted under IND 58,380 (the sponsor provides some regulatory history under this IND on page 131 in volume 1 of the submission). The most recent correspondence regarding pivotal trials to support a GAD indication is an Advice Letter dated 11/19/02 (responding to a 9/25/02 submission) with advice on primary variables for GAD trials. A 9/18/02 Advice Letter provides input on specific questions raised by the sponsor (refer to the 7/8/02, N226 submission under the IND) regarding their plans for submitting a supplemental NDA for GAD.

D. Related Reviews

As previously mentioned NDA 21-323 was recently approved for the indication of MDD (as well as the oral solution under NDA 21-365). Related NDAs are NDAs 20-822s and 21-046 for Celexa™ (citalopram hydrobromide, the racemate of SCT of) in tablet and oral solution formulations, respectively, which were approved for treatment of MDD. The date of approval for Celexa™ (NDA 20-822) for this indication was 7/17/98.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics, and/or other Consultant Reviews.

This submission has no new chemistry, preclinical or biopharmaceutical data. The CMC reviewer has not expressed any major issues so far in this review cycle. Biometrics is concurrently conducting a review of the statistical aspects of the efficacy data of the three pivotal GAD trials (SCT-MD-05, -06 and –07) provided in this supplemental NDA. Refer to Section X of this review describing critical biometric-related issues impacting on Clinical recommendations.

III. Human Pharmacokinetics and Pharmacodynamics

The following is a summary of the pharmacokinetic (PK) properties of SCT that described in current approved Lexapro™ labeling. The major pharmacodynamic (PD) properties of the drug are previously described and the submission does not provide any new information on PD.

A. Human Pharmacokinetics

The terminal half-life of SCT is about 27-32 hours with steady state levels achieved within approximately one week with daily administration. Single-dose and multiple-dose trials show linear and dose-proportional pharmacokinetics (PKs) in a 10 to 30 mg dose range. Tmax is 5±1.5 hours with no food effect on plasma levels. The oral tablet has an 80% relative biovailability compared to an intravenous dose.

The biotransformation of SCT is primarily hepatic. S-desmethylcitalopram (S-DCT) and S-di-DCT (SDDCT) are two active metabolites in which the latter is generally non-detectable in plasma of most subjects. S-DCT plasma levels are about one-third of SCT levels at steady state. *In vitro* S-DCT is 7 to 27 fold less potent than SCT as an SSRI. CYP3A4 and CYP2C19 are the primary isozymes for the N-demethylation of SCT. *In vitro* studies show no inhibitory effects on

hepatic isozymes tests (CYP3A4, -1A2, -2C9, -2C19, and -2E1). *In vivo* studies using a 20 mg dose fail to reveal a 3A4 inhibitory effect, but showed modest 2D6 inhibitory effects.

Because of AUC and T1/2 of SCT are each approximately 50% greater in elderly (≥65 year old) compared to younger subjects, the recommended starting daily-dose in elderly patients is 10 mg. This dose is also the recommended starting dose for patients with reduced hepatic function (based on PK studies of patients with reduced hepatic function treated with citalopram). A 17% reduction in clearance of citalopram was observed in patients with mild-moderate impaired renal function compared to normal controls. However, no dose adjustment is recommended. No gender effects on PK parameters are observed in a multiple-dose Phase I trial of SCT.

IV. Description of Clinical Data and Sources

A. Overall Data: Materials from NDA/IND

The following items were utilized during the course of this clinical review:

Documents Utilized in Clinical Review	
DATE	DESCRIPTION
November 26, 2002	• NDA 21-323 SE1-003, Hard copy clinical volumes (62 volumes) that included Case Report Forms. Case Report Tabulations were submitted as SAS Transport files on Compact Disk. • 1/7/03 BM supplemental amendment in response to inquires. • 3/12/03 BM supplemental amendment in response to additional inquires. • 2/11/03, 3/25/03 amendment (BM) submissions in response to inquiries and to provide additional information.

B. Tables Listing the Clinical Trials

Table IV.B.1. Clinical Studies Reviewed from this Submission

Protocol No	Study Design	Treatment Groups	N (Randomized) per Treatment group	N (Completers) per Treatment group (% of ITT Efficacy Pop.*)	N (ITT Efficacy Pop.) * per Treatment group	N (ITT Safety Pop.) ** per Treatment group
SCT-MD-05 **8-Week GAD*** Trial**	Multicenter, Double blind, Randomized, Flexible dose, Parallel group 25 U.S. sites****	Placebo group 10-20 mg/day SCT	128 129 **Total: 257**	95 (74%) 97 (77%) **Total: 192**	128 124 **Total: 252**	128 126 **Total: 254**
SCT-MD-06 **8-Week GAD*** Trial**	Multicenter, Double blind, Randomized, Flexible dose, Parallel group 19 U.S. sites****	Placebo group 10-20 mg/day SCT	145 149 **Total: 294**	114 (80%) 118 (81%) **Total: 232**	138 143 **Total: 281**	142 145 **Total: 287**
SCT-MD-07 **8-Week GAD*** Trial**	Multicenter, Double blind, Randomized, Flexible dose, Parallel group 23 US sites****	Placebo group 10-20 mg/day SCT	159 161 **Total: 320**	123 (78%) 119 (75 %) **Total: 242**	153 154 **Total: 307**	157 158 **Total: 315**
		Grand Totals:	**N=871**	**N=666**	**N=840**	**N=856**

*ITT Efficacy population: randomized subjects having at least one dose of double blind study drug and at least one post-baseline Hamilton Anxiety Rating Scale assessment.
**ITT Safety Population: randomized subjects having at least one dose of double blind study drug.
***GAD = Generalized Anxiety disorder
**** Only sites with randomized subjects are enumerated in this table.

C. Post-Marketing Experience
SCT is approved for marketing in 8 countries (as of the July 1, 2002 cut-off date): Austria, Denmark, Iceland, Lithuania, Norway, Sweden, Switzerland and the United Kingdom. Approximately 12, 700 patients received the marketed drug between the dates of 1/1/2002 and 7/1/2002. See section VII.M in this review for postmarketing safety observations.

D. Literature Review
For the purposes of this review, the sponsor appears to have conducted an adequate literature search for SCT (given the number of databases, the start dates and the search terms employed as shown below).

The sponsor conducted the literature search for the period from 2/1/02 (cut-off date for their 2/19/02 Safety Update submission under the original NDA) to 8/30/02 using the terms and databases itemized below.

Databases:
- MEDLINE (1966- present)
- TOXLINE (1965- present)
- BIOSIS (1969 – present)
- International Pharmaceutical Abstracts (1970-present)
- EMBASE (1974-present)
- Derwent Drug File (1983-present)

Terms:
- (S()Citalopram or
- (enantiomer and citalopram) or
- escitalopram or
- LU()26()054

Refer to section VII.M for the results of this search.

V. Clinical Review Methods
A. Materials Reviewed.
Refer to Section IV, above, regarding materials utilized for this review and for a summary of the clinical trials described in the submission.

B. Adequacy of Clinical Experience.
The sponsor makes their claim for the efficacy of SCT in the treatment of GAD in which they describe results of three multicenter, placebo controlled, 8-week GAD trials (SCT-MD-04, -05 and -06). These studies were virtually identical in study design using a flexible dose, parallel group design with a total of 871 randomized Ss among the three trials (see previous Section IV for table of all clinical trials). Section VII of this review (Integrated Safety) provides more information on the demographic features and the extent of drug exposure in the study population. Given these trials, along with previous trials under the Lexapro® and Celexa® NDA's, the data in the current supplemental NDA 21-323 submission are adequate to review.

C. Data Quality and Completeness

This section describes various comparisons made between sections of the submission which are described in more detail, below. These comparisons generally revealed adequate accuracy, consistency and content of information. On the basis of these observations, the quality and completeness of the data described in the submission appears to be adequate.

Each item below describes various comparisons and the results of these comparisons regarding their consistency and accuracy:

- Narratives of selected Ss with SAEs (those described in Table VII.E.2 in the appendix) generally showed consistency with the listing of SAEs (by terms) provided in panels in the ISS and with descriptions of these Ss in the text in the section on SEAs in the ISS (in section 9.2 of the ISS).
- Investigator listings in Appendix II in each Study Report for each study was compared to the listing of investigators in a table enumerating randomized Ss and Ss in the ITT safety and efficacy populations (Table 1.1 in a 1/7/03 response submission, upon request). These principal investigators were also compared to those listed in the Financial Disclosure section of volume 1 of the submission (Attachments A and B of this section). These three sources of investigator listings were consistent, except for a few sites that were not listed in Table 1.1 (this table enumerated only randomized Ss) as follows:
  - Study site 2 of Study SCT-MD-05 was not listed in Table 1.1 but was in the study report Appendix II and in the Financial Disclosure section
  - A study site 2 for Study SCT-MD-06 was not in Table 1.1, the study report or financial disclosure listings
  - Study sites 9 and 10 for Study SCT-MD-07 were not listed in Table 1.1 but were in the Study Report and the Financial Disclosure section.

The sponsor was inquired about the above 4 study sites and study site listings or tables. In a 3/12/03 amendment submission the sponsor explained that all 4 sites were terminated. Three of these terminated sites had IRB approval but had no randomized Ss prior to closing these sites. The fourth site did not complete their "paperwork" or final documents were not available and was therefore was not listed in all three listings (as above). The total number of randomized Ss shown in Table 1.1 was also consistent with the total number of randomized Ss for each study, as described in each study report. This observation is consistent with the 4 sites in question, as not having any randomized Ss. Consequently, the above observations do not impact on the overall study results.

- In a 1/7/03 response from the sponsor to inquiries for more information on these SAEs the sponsor indicated that the investigator changed the 2 of these SAEs, as follows:
  - #2116: pulmonary embolism was changed to "pneumonia" after performing tests at the hospital (note that the S was hospitalized in[redacted] and cut-off dates of safety results in the original submission are 12/2/01-7/1/02). This S received amoxicillin and no anticoagulants.
  - #2230: deep venous thrombosis (DVT) was changed to "musculoskelatal pain" since a Doppler test was negative for DVT.

In a 3/12/03 submission in response to further inquiry regarding SAE listings and subsequently changing SAE terms (not reflected in the original submission), the sponsor verified that no other SAE terms were changed.

D. Evaluation of Financial Disclosure

Nine investigators indicated they had financial arrangements. These 9 investigators were among a total of 67 investigative sites[1] (each with multiple investigators) that had randomized subjects among the three 8-week clinical GAD trials (MD-05, -06, and –07). All nine investigators checked the second box (type of) financial arrangement on Form 3455 (3/99). Each of the nine investigators had only approximately two to six randomized Ss in each treatment group (or 3-4% of all randomized Ss/group) for a given site or study (two of these investigators were sub-investigators at their respective sites). The sponsor was unable to obtain information from a small subset of sub-investigators despite "due diligence" in seeking the information. It is noted that any potential bias in the clinical trials was minimized for reasons such as the following: studies were double-blind, multi-center, conducted by multiple investigators, sites were independently monitored, and randomly audited by Forest, among other reasons.

VI. Integrated Review of Efficacy

A. Review of Studies for Which Efficacy Claims Are Made

The sponsor describes three placebo-controlled, double-blind, multicenter, randomized studies (SCT-MD-05,-06,-07) that employed a flexible dose design (10-20 mg SCT/day over an 8-week treatment phase) that showed significant improvement (from baseline to treatment endpoint) on the mean score of the Hamilton Anxiety Rating Scale (HAMD) in the SCT group compared to placebo. The total number of randomized outpatients with GAD in these three trials, combined, was approximately 870.

B. Pivotal Flexible Dose Trials on the Efficacy of Lu 26-054 (SCT) Compared to Placebo in the Treatment of Generalized Anxiety Disorder (Studies SCT-MD-05, -06, -07)

1. Investigators and Sites

See Tables VI.B.1-3 in the appendix for a listing of investigators/sites for Studies MD-05, -06 and –07, respectively (as provided in the Study Report volumes). The total number of sites with randomized Ss in each of these three trials was 25, 19 and 23 in each study, respectively (as shown in Table IV.B.1 in section IV.B). As previously noted, discrepancies between investigator site listings were found within the submission that were later clarified in a 1/7/03 submission (refer to Sections V.C. and V.D. above, for details).

2. Objectives

The objective of each study was to compare flexible dose (10-20 mg/day) SCT treatment to placebo on efficacy and safety in patients with GAD.

3. Fixed Dose Study SCT-MD-01: Study Population

Each treatment group consisted of 124 to 154 Ss among the three pivotal trials. To be eligible for the study Ss had to be 18 to 80 years old, generally healthy (as specified in the eligibility criteria) and meet DSM-IV criteria for GAD. Additional key inclusion and exclusion criteria are listed below (refer to the study reports for a complete listing).

Additional key inclusion criteria are outlined in the following.

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[1] as clarified upon request in a 1/7/03 amendment submission.

Subjects were required to have each of the following rating scores at screening and baseline visits:

- Hamilton Anxiety Rating Scale (HAMA) score of ≥18 and on each of the tension and anxiety items, must have a score of ≥2
- Hamilton Depression Rating Scale (HAMD) score ≤ 17
- Covi Anxiety Scale score > Raskin Depression Scale score

Some of the key criteria leading to exclusion were that the S:

- Met DSM-IV criteria for any of the following disorders:
  a) Bipolar disorder
  b) Schizophrenia or any Psychotic disorder
  c) Obsessive Compulsive disorder
  d) Mental Retardation, Pervasive Developmental disorder, or Cognitive disorder
  e) Substance Abuse/Dependence within 6 months of study entry
- Had a principal diagnosis of any Axis I disorder (DSM-IV) except GAD
- Had any history of a Psychotic disorder (DSM-IV)
- Had psychotic features
- Had a Personality Disorder to the extent that it would interfere with their participation in the study
- Was a suicide risk or made a serious suicide attempt within one year prior to study entry
- Did not meet restrictions on concomitant medications (see section below on concomitant medications)
- Failed to respond to an "adequate trial" of citalopram or to adequate trials of two other SSRIs
- Received ECT therapy within 3 months prior to study entry
- Required psychotherapy or behavioral therapy during the study
- Tested positive on the urine drug screen

Permitted and Prohibited Concomitant Medications
The following were prohibited, as specified:

- Depot neuroleptic within 6 months prior to study entry
- Psychotropic medications except zolpidem for sleep including drugs with a psychotropic component
- Any neuroleptic, antidepressant or anxiolytic agent within 2 weeks (5 weeks for fluoxetine) prior to start of double blind treatment phase of the study
- Used any benzodiazapine within one month prior to the initiating the double-blind treatment phase of the study
- Refer to the submission for a complete listing of prohibited, as well as permitted concomitant medications.

4. Study Design

Each study was a randomized, placebo controlled, multi-center, flexible dose (10-20 mg daily dose, p.o.), parallel group study involving a one-week single blind placebo lead-in phase

followed by an 8 week double-blind treatment phase upon which Ss were randomized (1:1) to one of the following treatment groups (oral administration):

- SCT group (10-20 mg/day). Ss started at the daily dose of 10 mg (one tablet/day) which could be increased after 4 weeks to a daily dose 20 mg (two tablets a day) in Ss with an inadequate response to the lower dose (as judged by the investigator).
- Placebo group. After 4 weeks of double-blind treatment of one tablet a day, the dose could be increased to two tablets a day if the S was judged by the investigator to have an inadequate response.

Dummy dosing was employed. Ss were instructed to take their daily dose in the evening, but could switch dosing to the morning as they preferred. The minimum and maximum daily doses that were permitted during the double-blind treatment phase were one and two tablets, respectively. Ss receiving 2 tablets daily could have the dose reduced to one tablet daily due to AEs at any time. Refer to Table VI.B.4 in the appendix for a flow chart of visits and time-points for obtaining safety and efficacy measures (as provided by the sponsor). The next section lists the efficacy and safety measures (section 5, below).

5. Assessments Employed

As shown in the Schedule of Evaluation, Table VI.B.4 (in the appendix, as provided by the sponsor) various assessments were conducted at screening, baseline (following a one-week single blind placebo run-in phase), and on weeks 1, 2, 4, 6 and 8 during the 8 week treatment phase (or upon early termination).

Primary Efficacy Assessments.

HAMA (14-item scale)

Secondary Efficacy Measures:

- HAMD
- Hospital Anxiety and Depression Scale (HAD)
- Clinical Global Impressions Scale for Improvement (CGI-I) and for Severity (CGI-S)
- Covi
- Raskin
- Others (refer to submission)

Safety assessments:

- Recording of adverse events
- Vital signs (including body weight)
- Physical examination
- 12-lead ECG
- Laboratory parameters:
  - Hematology, blood chemistry screen (includes measures of renal function, electrolytes, glucose, liver function tests, among others)
  - Urinalysis
  - Serum beta-HCG in women of childbearing potential at screening only
  - Thyroid Function Test at screening only
  - Urine drug screen at screening only

In addition to the safety assessments conducted at screening and baseline visits, as above, a psychiatric evaluation was conducted at screening that included a Mini International Neuropsychiatric Interview (MINI).

6. Analysis Plan

Dataset Analyzed. The ITT Efficacy dataset was analyzed (data from Ss who had at least one dose of double blind study drug and at least one post-baseline HAMA assessment). The last observation carried forward (LCOF) dataset was used for the primary analysis, but the observed cases (OC) dataset was also analyzed.

The primary efficacy variable was as follows:

- The mean change from baseline to treatment endpoint (week 8) on the HAMA total score.

The secondary efficacy variables are listed below.

a. Mean change from baseline to treatment endpoint (week 8) on the following scores:
  - HAMA Anxiety item score
  - HAMA Tension item score
  - HAMA Psychic Anxiety subscale score
  - HAMA somatic anxiety subscale
  - HAD anxiety subscale
  - Covi Anxiety scale
  - CGI-S
  - CGI-I week 8 score
  - HAMD 17-item

b. Mean change from baseline to treatment endpoint (week 8) on the following scores that were generally developed to reflect depressive symptoms:
  - HAMD
  - HAD depression subscale
  - Raskin

Statistical Tests Employed. Treatment and center main effects and interaction effects analysis of covariance (ANCOVA) model was employed covarying for the baseline measure. Since the CGI-I is a score on improvement relative to baseline (a baseline measure is not applicable), this secondary efficacy variable was analyzed using a treatment by site analysis of variance (ANOVA) model. Results are provided as values obtained from a SAS Type III analysis, calculating the difference between two treatment groups using the least square means (unless otherwise specified).

7. Patient Disposition

Refer to Table IV.B.1 (above in Section IV.B) for the sample size of randomized Ss, completers, Ss in the ITT safety and efficacy populations for each treatment group of each study. A total of 871 Ss were randomized to the double-blind treatment phase, 856 Ss received at least one dose of double-blind study drug (the ITT Safety Population) and 840 Ss also received at least one post-baseline HAMA assessment (the ITT Efficacy population). Fifteen randomized Ss were not included in the ITT Safety population because of either being lost to follow up or failing to take

the double-blind study drug. Sixteen additional Ss were not included in the ITT Efficacy population because these Ss did not have at least one post-baseline HAMA assessment.

Tables VI.B.5-7 in the appendix, summarize the enumeration and disposition of the ITT Safety population for each trial (as provided in the submission). In summary the treatment groups were generally similar in the distribution of subjects among various categories of reasons for early withdrawal from the study. However, SCT Ss showed numerically higher incidence rates on withdraw due to an adverse event and lower incidence rates of Ss withdrawing due to lack of efficacy (in 2 trials) compared to the incidence of placebo Ss in each of these categories, respectively. Two trials (MD-05 and –06) also showed higher incidence rates for withdrawal of consent in SCT Ss compared to placebo Ss. None of these differences were reported as being significant differences, except for the following. The exception was in Study MD-05 in which the incidence of dropouts due to an adverse event was significantly greater in SCT Ss (11%) than in placebo Ss (3%).

8. Baseline Demographics/Medical/Psychiatric Comorbidity and Baseline Efficacy Measures

Baseline Demographics. Section VII B provides a table of demographic features of each treatment group (ITT Safety Population) for the three trials, combined. As shown in this table, the mean age of Ss was 39 years old (range of 18 to 79 years old) with the majority of Ss being over 60 years old (93%), female (56%) and Caucasian (79%). Mean body weight of the Ss was 171±43 pounds (range of 85 to 359 lbs). Treatment groups within and across studies were generally similar on these demographic parameters (mean age and weight, proportion of Ss by gender and by race: Caucasian versus non-Caucasian) with a few exceptions. Treatment groups in Study MD-06 showed significant differences on gender (incidence of females was 61% and 49% in the SCT and placebo groups, respectively, $p<0.05$) and almost significant differences on mean weight (9 lbs greater weight in the placebo group compared to the SCT group, $p=0.052$). However, the level of significance for these comparisons is without a correction for multiple comparisons.

Medical and Psychiatric Comorbidity. Treatment groups in each study were not significantly different of the mean duration or age of onset of GAD (the mean duration was approximately 9 to 12 years and the mean age of onset was approximately 28 to 30 years old among the three studies for the ITT Safety population). Treatment groups did not show significant differences on the incidence of secondary psychiatric disorders in each study. Approximately 32 to 40% of the Ss among the three trials had either a past history or ongoing concomitant psychiatric history with the majority of these Ss having "depression" or a non-GAD anxiety disorder, as in the following. The approximate incidence rates (ITT Safety population among the three trials) of the following concomitant psychiatric disorders are noted:

- Ongoing Major Depressive disorder (MDD): 5 to 8% of Ss (22-26% with either ongoing or past history of depression)
- Ongoing non-GAD anxiety disorders: 7-11% (10-16% with either ongoing or past history of non-GAD anxiety disorders)

Treatment groups were similar on across studies on mean and median scores of the following efficacy measures at baseline:

- HAMA scores (approximately 22±4 mean total score points and 22 median score points in each treatment group of each study)
- HAMA anxiety or tension items (each item was approximately 2.7±0.5 mean total score points and approximately 3 median score points in each treatment group of each study)
- CGI-S scores (approximately 4.2±0.5 mean total score points and approximately 4.0 median score points in each treatment group of each study)
- HAD Anxiety subscale (approximately 12 to 13±4 mean total score points and approximately 12 to 13 median score points in each treatment group of each study)
- HAMD scores (median and mean values were generally 12-13, and individual subject values generally ranged from 1-17 in each study, noting that 17 as the maximum allowed score to be included in the study)

Concomitant Medications.
Treatment groups of the ITT Safety population (the three studies combined) were generally similar in the percentage of subjects taking concomitant medications during the double-blind treatment phase of the study (approximately 83 to 86%/group). Treatment groups were generally similar in the distribution of Ss across various medication categories. Common (≥10% in any of the groups) concomitant medications were the following (approximate percentage of users/group):

- Anti-inflammatory and anti-rheumatic products: 35 to 39%/group
- Analgesics: 36 to 38%/group
- Vitamins: 24% to 26%/group
- Antacids: 11-15%/group
- Endocrine therapy (in female Ss, only): 13 to 14%/group
- Psycholeptics: 12%/group
- Systemic Anti-histamines: 12%/group

9. Efficacy Results
Results on the Primary Efficacy Variable: the mean change from baseline to treatment endpoint (week 8) on the HAMA.

See the Table VI.B.8 in the appendix (as provided in the submission) showing the results on the primary efficacy variable. As shown in this table significantly greater improvement from baseline to treatment endpoint (Week 8 visit) was observed in the SCT group compared to the placebo group in each of the three trials (p values ranged from 0.05 to 0.01 with mean decrease in the score ranging from –9.2 to –11.3 in the SCT group and from –7.4 to –7.7 in the placebo group).

Figure VI.B.9 in the appendix (as provided by the sponsor) shows results of the primary efficacy variable by study visit for each treatment group. This figure shows the results from the 3 trials, pooled and shows consistently greater improvement over each visit (LOCF dataset). Similar results were generally observed for each individual study.

The above results were those of the LOCF dataset. When analyzing the OC dataset, similar results were revealed for both mean change from baseline to treatment endpoint and when examining treatment group effects at each time-point (at each visit).

Secondary Efficacy Variables.

Results on Measures Designed for Assessing Anxiety Symptoms. Table VI.B.10 (as provided by the sponsor) shows at least numerical trends for greater improvement from baseline to Week 8 assessments in the SCT group compared to placebo on each of the mean HAMA psychic anxiety subscale, CGI-S and CGI-I scores in each study (LOCF, ITT dataset). Similar results were observed with mean scores on each of the following: the HAD anxiety subscale, HAMA tension item and the HAMA anxiety item.

Results on Measures Designed for Assessing Depressive Symptoms.
Trends for greater improvement or significantly greater improvement on some of the scales or subscales for depression was reported (e.g. HAMD, HAD depression subscale or the Raskin).

Results on Patients With or Without a Concomitant Secondary Diagnosis of Major Depressive disorder. Only 7% of Ss had MDD (approximately 28 Ss in each placebo and SCT group for all 3 trials, pooled) had secondary concomitant diagnosis of MDD. Given the small number of Ss with MDD, the results of a statistical analysis conducted by the sponsor to examine potential treatment group by concomitant MDD interaction effects on the on the primary efficacy variable are not described for the small subgroup. However, their results from a statistical analysis of the larger subgroup of Ss without MDD (approximately 390 Ss/treatment group, in the pooled studies) revealed a numerically greater improvement in the SCT treated Ss compared to placebo on mean change from baseline to treatment endpoint on the HAMA total score (a mean change of -10.1 ± 0.4 and -7.7 ± 0.3 in the SCT and placebo groups, respectively).

Results on Patients Classified into High or Low Scorers on the HAMD.
The sponsor classified Ss into high and low HAMD scorers (using the median baseline score of 12 as the cut-off score in which high scorers had HAMD>12). A reanalysis of results on the primary variable (mean change from baseline to treatment endpoint on the HAMA score) for these subgroups of each treatment group (for the three GAD trials combined) revealed similar results to those of the primary analysis. As shown in Table I.2D in the ISE of the submission, mean changes of -10.4 ± 0.4 (SEM) and -9.8 ± 0.5 in the low and high HAMD scorers of the SCT group, respectively, were observed compared to a mean changes of -7.3 ± 0.5 and -7.8 ± 0.4 in low and high HAMD scorers of the placebo group on the primary HAMA variable.

<u>Subgroup Analysis</u>
The sample size of Ss over 60 years old and Ss in non-Caucasian ethnic groups were not adequate for interpreting efficacy results analyzed on the basis of age or ethnicity.

An analysis on the basis of gender revealed no significant gender main effects or treatment group by gender interaction effects on the primary efficacy variable (LOCF ITT dataset; data from all 3 trials were pooled). Men and women showed similar mean HAMA scores at baseline, while noting that the sample size of women in each treatment group (approximately 236 Ss) was numerically larger than the sample size of men of each group (approximately 184 Ss) in the 3 studies, combined.

10. Conclusions

Each of three GAD trials showed significantly greater improvement on the mean change from treatment endpoint HAMA score in the SCT group compared to placebo. Secondary analysis provided further support for efficacy.

At least trends for greater improvement, or significantly greater improvement, was also observed on secondary measures of depressive symptoms in the SCT group compared to placebo in these trials. These secondary results on depressive symptoms, may be suggestive of pseudospecific effects. Depressive symptoms and comorbidity with MDD is fairly common among patients with GAD. Furthermore, SCT is approved for treatment of MDD. However, specific symptom items for anxiety or tension showed significantly greater improvement in the SCT Ss compared to placebo in the GAD trials. Low as well as high scorers on the HAMD scale also showed greater improvement on mean change in the HAMA score in SCT patients compared to placebo. Hence, secondary analyses supported a conclusion that effects were not secondary to improvement on depressive symptoms, but rather reflected improvement on GAD. Furthermore, subjects were screened for a primary diagnosis of GAD and eligibility criteria included cut-off scores on various anxiety and depression scales to screen for subjects with higher scores on scales for anxiety symptomatology in contrast to scores on scales for depressive symptoms. Finally, only 5-8% had ongoing Major Depressive Disorder.

Gender effects on efficacy were not observed. There were insufficient numbers of Ss who were elderly and insufficient numbers in ethnic group subcategories, for results of age-group or ethnic group analyses to be considered definitive or interpretable.

In conclusion, the three GAD trials support an overall claim for the efficacy of SCT (within the 10 to 20 mg daily flexible dose range) in the treatment of GAD.

VII. Integrated Safety Information

A. Background Information

The submission includes safety information for three groups of trials, as follows:

- Three pivotal completed GAD trials (MD-05, -06, and –07):
  a) Deaths, SAEs and ADOs (with narratives and CRFs).
  b) Integrated safety results. Thee safety results on the following variables were integrated by pooling data from the three GAD trials (using data from the ITT safety population): Adverse event results, results of clinical safety assessments (laboratory, vital sign and ECG results) for the ITT Safety population (for the three trials, combined are also provided, as described in this review. Demographic features, disposition of Ss and estimated exposure of the Ss of the ITT Safety population are also included (for the three trials combined).
- An ongoing GAD extension trial (SCT-MD-17) which is an open label, 24-week, extension study of 540 enrolled Ss (Ss who completed Studies SCT-MD-05, -06 and –07): deaths, SAEs and ADOs (with narratives and CRFs) as of July 1, 2002 are described in the submission.
- All other trials (designated as Other Trials in this review) that were active between December 2, 2001 and July 1, 2002 (SCT-MD-09, -10, -11: part of 11D, -12, -18, -20, -21, -26, 99269, 99270, and 99505): deaths and SAE (listings and narratives) that were reported within the cut-off dates. Only one of these trials (MD-20) was conducted on GAD patients (122 SCT treated Ss). This 26-week study did not include a placebo group (only an active comparator group). The other trials were primarily of patients with MDD and a few were of other non-

GAD populations. Most of these trials had an 8 to 24 or 26-week double-blind treatment phase.

Refer to Table IV.B.1 for the enumeration of subjects in the GAD trials in Section IV.B. of this review. The enumeration of Ss in the ongoing GAD trial (MD-17) and in the Other trials is provided in the following:

- Ongoing GAD trial MD-17: 540 enrolled who received SCT
- Other Trials: N=2010 with an estimated 1257 SCT Ss (although study drug is blinded in approximately 90% of the total 2010 Ss)

B. Demographic Characteristics

Demographic features in the Three GAD Trials, combined (Studies SCT-MD-05, -06, and –07). The table below summarizes the demographic features for the 856 Ss in the ITT Safety population. Treatment groups were generally similar on various demographic measures (age, race, proportion of Ss 60 years and older, and weight).

Summary of Demographic Features for Treatment groups of GAD Trials Combined (Studies SCT-MD-05, -06, -07)*			
	Placebo N=427	Escitalopram N=429	Total N= 856
Mean±SD Age (years)	40±13	39±13	39±13
Age range (years)	18-78	18-79	18-79
% of Ss < 60 years	93	93	93
% of Ss ≥ 60 years	7	7	7
% Male	46	42	44
% Female	54	58	56
% Caucasian	79	78	79
% Non-Caucasian	21	22	21
% Black	8	7	8
% Asian	3	4	4
% Other	10	10	10
Mean±SD Weight (lbs)	172±43	171±43	171±43
Range of Weight (lbs)	85-359	96-350	85-359
*This table is similar to Panel 11 volume 56 of the ISS.			

C. Extent of Exposure

Overall exposure in completed GAD trials, combined (MD-05, -06, and –07): The following shows exposure of the ITT safety population.

Overall Exposure of Subjects* in the GAD Trials (MD-05, -06, and –07)		
	Placebo N=427	Escitalopram N=429
Mean±SD Duration (days)	50±16	49±18
Median Duration (days)	56	56
Range (days)	1-70	1-89
Mean Patient Years**	58	58
Data source: Table 3.1 page 14 in the ISS.		

*Ss who received at least one dose of study medication

** Patient years = total time of exposure to study drug expressed in years.

Approximately 60% of Ss in the three GAD trials, combined (in the ITT safety population) were exposed to at least 56 days of assigned study drug in each treatment group. The mean daily dose in SCT treated Ss in the ITT safety population (N=429) was 12.7 mg.

Exposure in Completers in completed GAD trials. The following tables summarize exposure in completers.

Exposure of Completers in the Three GAD Trials, combined.		
Duration of Treatment (days)	**Placebo N=332 n (%)**	**Escitalopram N=334 n (%)**
29-56	83 (25)	75 (23)
≥56	249 (75)	259 (78)
Mean	57±3	58±4
Median	56	56
Range	48-70	43-89
Patient Years	51.9	52.6
Data source: Table 3.2 in ISS (page 15).		

Summary Statistics of Mean Daily Dose for Completers*

Protocol		*Treatment Group*		
		Placebo	**Escitalopram**	
		tablets/day	*tablets/day*	*mg/day*
SCT-MD-05	# completed	95	97	97
	Mean	1.38	1.35	13.5
	Median	1.46	1.46	14.6
	Min, Max	0.9, 1.8	0.9, 1.8	8.9, 17.8
SCT-MD-06	# completed	114	118	118
	Mean	1.36	1.35	13.5
	Median	1.46	1.47	14.7
	Min, Max	0.9, 1.6	0.9, 1.9	9.3, 18.8
SCT-MD-07	# completed	123	119	119
	Mean	1.37	1.30	13.1
	Median	1.46	1.42	14.2
	Min, Max	0.9, 1.6	0.9, 1.6	9.3, 15.8
Pooled	# completed	332	334	334
	Mean	1.37	1.33	13.3
	Median	1.46	1.46	14.6
	Min, Max	0.9, 1.8	0.9, 1.9	8.9, 18.8

*As provided upon request in 1/7/03 response submission to 12/18/02 and 12/23/02 inquiries (via e-mail).
Mean daily dose per patient is defined as the total number of tablets (or total mg) divided by duration of treatment.
Duration of treatment = Stop date – Start date of double-blind medication + 1.
In studies SCT-MD-06 and SCT-MD-07, each tablet in bottle B (escitalopram 20 mg tablets) dispensed at end of weeks 4 and 6 were counted as two tablets in the computation of mean daily dose.

Exposure in the Ongoing MD-17 GAD trial.
A total of 540 Ss had at least one dose of SCT corresponding to 173 estimated patient years.

Exposure in Other Trials.
A total of 2010 Ss received treatment between the cut-off dates (as previously specified). Approximately 90% of these Ss (n=1824) are in trials that are still blinded. Based on the randomization methods, it is estimated that 1257 Ss were treated with SCT (most trials employed at least 8 weeks of treatment).

D. Deaths
Three deaths occurred in SCT treated Ss and one death occurred in a S on blinded study drug (2 completed suicides, cerebrovascular accident with complications). These deaths, as summarized below, appeared to most likely be due to underlying pathology, ongoing illness and in the case of suicide, were also likely to be associated with lack of efficacy to ongoing treatment. A death occurred in a venlafaxine treated S (S3261) but is not described in this review which focuses on the safety of Lexapro.™
Completed GAD trials (SCT-MD-05, -06, and 07).
No deaths were reported.
Ongoing MD-17 GAD trial.
S5078: this S committed **suicide** and is likely to be reflecting underlying psychopathology and lack of efficacy of treatment (also reported in the 2/19/02 safety update submission under the original NDA).
Other Trials.
S5612 (Study 99258) was a 76 year old female with MDD, hypertension (since 1978) who received 261 days of study drug when she had a **cerebrovascular accident** (CVA). She was hospitalized in a coma with respiratory distress. The following additional conditions occurred during her hospitalization: pneumonia, incomplete right bundle branch, several "cerebral thromboses," septic shock, fever and hypotension and ultimately death (3 days after she was admitted). The patient had multiple risk factors for these events that included her age, a history of hypertension, and multiple concomitant cardiac-related medications, among other possible risk factors. Given the duration of treatment on the study drug (261 days) before she had the CVA and the presence of potential risk factors, the events that she experienced and her death were not likely to be due to SCT treatment.

S2113 (Study 99505) was a 77 year old female with MDD, history of hypertension, obesity, non-insulin dependent diabetes mellitus, and hypercholesterolemia. She received 150 days of study drug, when she **died in her home**, specified by the investigator **as a "natural course."** She had no AEs at her last study visit, which was one week before her death. Upon request, the sponsor provided additional information (in a 1/7/03 response). No autopsy was performed on this S and the additional information failed to reveal any clear causes of her death. This patient had multiple underlying conditions and risk factors that were likely associated with her death. Furthermore, the long period of treatment and the absence of reported AEs, one week before her death, would suggest that this is not drug-related. However, one possible consideration could be that this patient committed suicide that was not detected, but the information provided on this subject suggests that this possibility was not suspected (i.e. the narrative did not describe any suicidality or evidence of suicide in this subject).

E. Serious Adverse Events (SAEs)

Completed GAD trials (SCT-MD-05, -06, and 07). Only one S (S7013) out of 429 SCT treated Ss of the ITT Safety population had a SAE (an additional S had an SAE during the placebo lead-in period of suicidal tendency). S7013 (Study MD-07) had hypertension (210/110 mmHg) on Day 12 of SCT treatment that lead to hospitalization in discontinuation of the study drug. However, given that she had preexisting hypertension and the presence of hypertension upon assessment at baseline, this event was likely due to her pre-existing condition.[2] Furthermore, clinical trials of SCT, citalopram (as in current labeling) or other SSRIs do not show evidence for hypertensive effects with this drug class.

Ongoing MD-17 GAD trial. A listing of SAEs is provided in Table VII.E.1 in the appendix (as provided by the sponsor). S5078 (committed suicide) was previously described under subsection D on deaths. In summary these SAEs appeared to be more likely due to at least one of the following conditions: due to underlying or pre-existing conditions, risk factors, accidental injury that did not appear to be drug-related, or were conditions such as neoplasia (that do not appear to be consistent with an effect from short-term treatment and some Ss had pre-existing signs and symptoms). Selected SAEs (diabetes mellitus in S6019, increased liver function tests in S7108 are described in Table VII.E.2 in the appendix of this review).

Other Trials. SAEs are listed in Table VII.E.3-4 (as provided by the sponsor). Note that Table E.4 was submitted in a 1/7/03 amendment submission for Ss in which study drug was subsequently unblinded (after the cutoff date used for the original submission). Two deaths (S2113 and S5612) listed in Table VII.E.3 are previously described (see subsection D, above). Based on the listing and a review of selected narratives (see Table VII.E.2 in the appendix for details on selected SAEs), the majority appeared to be due to underlying or pre-existing conditions (and lack of efficacy for those involving psychopathology), or were not unexpected for the study population or for the study drug (e.g. rash). However, a potential role of study drug cannot be ruled out.

Hypomania occurred in S1184 resulting in termination of treatment. This event could be due to underlying, undiagnosed bipolar (as is no uncommon in this patient population) but could be drug-related. A section of current labeling addresses the potential for activation of mania. S8041 who had the SAE of pulmonary embolism of unclear etiology, as described below in which the study drug remains blinded at this time. Refer to Table VIIE2 for a description of selected SAE's.

Pulmonary embolism (PE) was reported as an SAE in **S8041** in which the etiology remains unclear and study drug is blinded. This S was a 36-year-old female who appeared to be healthy and was receiving no concomitant medication. Although the S received heparin followed by 6 months of coumadin, the MedWatch report (provided by the sponsor) does not describe any diagnostic tests to confirm or rule out PE. Due to paucity of information in this S and that she

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[2] S7013 (Study MD-07) was a 58 year old female with a history of hypertension, who had high blood pressure (160/96 mmHg) at baseline. On Day 12 of treatment she had a blood pressure of 200/110 mmHg along with disorientation, dizziness and headache resulting in hospitalization in discontinuation of the study drug. The dose of her metoprolol was increased and amlodipine besilate and an ACE inhibitor were prescribed. Her symptoms and hypertension resolved within approximately one day of this treatment regimen, except for the headache.

had no reported risk factors or pre-existing conditions, a possible role of SCT cannot be ruled out. Yet, the study drug remains blinded. PE is not known to be associated with SSRIs or with SCT. Refer to Table VII.E.2. for further details on this S.

Pulmonary embolism and deep venous thrombosis were SAEs reported in two additional Ss who were non-elderly women. Upon inquiry to the sponsor about these Ss, the sponsor reported that the investigator subsequently changed these SAE terms. The new SAE terms are **pneumonia and musculoskeletal pain** in the Ss, respectively (as described in a 1/7/03-amendment submission in response to inquiries). This new information, which also included the unblinded study drug, failed to reveal any new or unexpected events for the study population or for SCT (or other factors were revealed that may be playing a role).[3]

F. Dropouts due to Adverse Events

Results from GAD trials on adverse dropouts (ADOs) generally did not reveal any remarkable, or unexpected events that are either generally observed in the study population, during treatment with SCT or with other SSRIs.

An ADO due to elevated LFTs (S6155) and an ADO (S7110) due to first degree AV block (a PR interval of up to 220 msec) were events that showed a temporal relationship with SCT treatment that was suggestive of the events being drug-related. Both events occurred during the GAD extension study (Study MD-17) and were not SAEs (Ss did not appear to have associated AEs or the events appeared to be moderate or mild in nature). The "Other Events Observed During the Premarketing Evaluation..." section of current approved Lexapro™ labeling includes "abnormal ECG" as an infrequent event. This same section in proposed labeling now includes "hepatic enzymes increased" as an infrequent event.

The results on dropouts in various trials are described in more detail below.

Completed GAD trials (SCT-MD-05, -06, and 07).

The following are common ADOs (incidence of >1%) that occurred in either treatment group in the three GAD trials, combined (incidence in placebo and SCT groups provided):

- All ADOs (4%, 8%, respectively)
- Nausea (0%, 2 %, respectively)
- Headache (1%, 1%)
- Insomnia (0, 1%)
- Fatigue (0%, 1%)

The data source of the above is Panel 17 in the ISS.

Only 1 ADO was also a SAE which was hypertension (S7013), as previously described under subsection E.

Tables VII.F.1-3 in the appendix, list individual ADOs for each of the 3 GAD trials (as provided by the sponsor).

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[3] SAEs that were later changed. **#2116: "pulmonary embolism"** (reported on Day 212 of SCT treatment) was **changed to "pneumonia"** after performing tests at the hospital. This 39 year old S (in study 99505) received amoxicillin and no anticoagulants. This S also had non-accidental overdose as an SAE of Day 100 of treatment. **#2230: deep venous thrombosis (DVT)** was changed to **"musculoskelatal pain"** since a Doppler test was negative for DVT. This 50 year old S received paroxetine.

Ongoing MD-17 GAD trial.
Only insomnia and ejaculation disorder were common ADOs in Study MD-17 (1.3% and 1.6%, respectively, among 540 Ss). Selected Ss with ADOs are described below (first degree AV block and elevated liver function tests). These ADOs may be drug related and are not described in labeling (other than under the section on "Other Events Observed During the Premarketing Evaluation…").

Selected ADOs
S7110 had **first degree AV block** that appeared to be asymptomatic (this S had AEs but they appeared to be unrelated to the ECG results). No other ECG abnormalities were described. This event appeared to be drug related since it showed the following temporal relationship with SCT treatment. The event was not observed at baseline (PR interval of 208 msec), but appeared during treatment (PR interval of up to 220 msec) and then resolved within a few days after treatment cessation (PR of 207 msec, similar to the baseline value). However, according to a cardiology assessment approximately 3 weeks later (post-treatment), first degree AV block was "confirmed," suggesting that the S may have a pre-existing condition. No data or a copy of the ECG could be found, except for the PR interval which was only 211 msec. This PR interval value is similar to pre-treatment and post-treatment values. This S is described in more detail in Table VII.F.4 in the appendix of this review. While this event could be drug-related, asymptomatic AV block is not uncommon and frequently benign in the general population (e.g. athletes, the young or indicative of increased vagal tonicity).

Elevated LFTs is observed in some SCT Ss. S6155 had mildly increased LFTs that appeared to be asymptomatic and were serendipitously revealed as part of following the protocol for entering into the extension study. This ADO (in the absence of diagnostic or other information) appeared to be drug related. The S is described in more detail, below. One SAE (S7108) had elevated LFTs that appeared to be due to a viral CMV hepatitis (as previously described and as in Table VII.E.2 in the appendix).

SAEs and ADOs reported in depression trials supporting the Major Depressive disorder indication for Lexapro™ (including a longer term trial) only had one S (S2071) with increased LFTs that appeared to be drug-related. This was an ADO due to a 3-6 fold increase in LFTs from baseline values (refer to 10/19/01, 11/19/01 reviews under 21-323 and in a 3/8/02 review under 21-440). This S was a 40 year old female who received 51 days of citalopram followed by 51 days of open label SCT when liver enzymes were elevated (baseline levels were within normal limits) to the following values: 74 IU/l (SGOT), 149 IU/l (SGPT) and 492 IU/l (LDH). LFTs normalized within 4 days after treatment cessation.

The sponsor has increased hepatic enzymes added to the list of "Other Events Observed During the Premarketing Evaluation of Lexapro.™"

S6155 with elevated LFTs in MD-17: This S was a 45 year old female with GAD and no other medical conditions or concomitant medical conditions. She had a total of 66 days of SCT (8 days of SCT in MD-17, preceded by 58 days during the lead-in study MD06). At baseline of study MD-06 LFTs were within normal limits. On the day of starting treatment in MD-17 ALT and AST were 100 and 77 U/l, respectively and increased further after approximately one week (114 and 92 U/l, respectively) upon which treatment was terminated. Follow-up assessments

showed gradual return to within normal limits by approximately 5-6 weeks after treatment cessation. In the absence of any other information, the absence of concomitant medications and given the temporal relationship between SCT treatment and elevated LFTs this ADO appears to be drug-related. However, it was mild in nature and the subject was asymptomatic.

G. Specific Search Strategies
Special Populations.
Patients with a History of Cardiovascular or Neurological Disorders. The sponsor determined the incidence of AEs of each treatment group for two special patient populations in the GAD trials, combined. These populations were patients with a history of cardiovascular disease (CVD) and patients with a history of neurological disorders (ND). A total of 114 placebo Ss (out of 427 placebo ITT safety Ss) and 101 SCT Ss (out of 429 SCT ITT safety Ss) had history of CVD and a total of 230 placebo Ss and 254 SCT Ss had a history of ND.

The common AEs (5%) in the SCT CVD or ND groups were generally similar to those observed for all SCT Ss. However, these results can only be considered preliminary. The studies were not specifically designed for determining drug effects on safety in special populations, and other methodological limitations existed in the trials. For example, the CVD and ND populations were heterogeneous populations, as Ss with specific disorders were pooled (given that the sample sizes were generally not sufficient for examining specific patient subgroups).

Bradycardia and QT Prolongation. Evidence for a decrease in heart rate and prolongation of QT is reported for both citalopram and SCT (refer to Celexa® and Lexapro® labeling describing a small effect observed in mean changes in heart rate and in QTc interval and on the incidence of heart rate and QTc outliers). Therefore, this subsection addresses the potential safety concern regarding bradycardia and QT prolongation. QT prolongation or bradycardia were not reported in any CVD SCT Ss (upon inspection of Table 9.1 of the ISS).

None of the SAEs in the three GAD trials were associated with related cardiovascular events except for hypertension (the only SAE reported in these trials). Similarly an examination of the line listing of ADOs in the three GAD trials (Table 4.4 of the ISS) failed to show cardiovascular related events such as bradycardia, syncope, abnormal ECG, QT prolongation.

The following are some relevant events reported in the three GAD trials. One ADO (S5065) had a baseline heart rate of 60 which decreased to 48 on week 2 of treatment and one week later (2 days after cessation of treatment), but did not appear to have associated AEs. The AEs resulting in termination of treatment were a metallic taste and nausea and did not coincide with the full period of decreased heart rate (started after the onset of bradycardia and resolved before resolution of the bradycardia). This subject is also described in the previous section on ADOs (Section VIIF). S5049 in Study MD-05 had a baseline HR of 60 bpm who's HR decreased to 40, 44, and 44 on weeks 2, 4, and 6 of SCT treatment. HR was 50 bpm at the end of the study. No AEs associated with the decreased HR were reported and the S completed the study, as well as continuing into the extension trial (MD-17). This subject is also described in the section on vital signs (Section VII J.). Dizziness was reported in only a few SCT Ss, as well as in several placebo Ss as events that resulted in an ADO and were generally associated with other non-cardiac related AEs.

Syncope was reported as an AE in only 1 SCT patient with CVD in the 3 GAD trials. Syncope was not associated with any ADOs or SAEs in the three GAD trials. S5054 in Study MD-05 had an AE of syncope 2 days after starting SCT (also had nausea, dry mouth, insomnia and dizziness at the time). Vital sign and ECG data during this event were not obtained (see the 3/12/03 submission in response to inquiries on this S). However, vital sign data within 5 days after this event and ECG data collected at treatment endpoint (at 8 weeks of treatment) were similar to baseline values. This S had bradycardia at baseline in which the HR was 56 bpm and was also 56 bpm when the S was assessed 5 days after the syncopal event.

Abnormal ECGs were reported in some Ss in the 3 GAD trials, but did not appear to be remarkable and did not appear to show differences between placebo and SCT groups, as follows. An abnormal ECG was reported in 1 SCT and 1 placebo S. However, abnormal ECGs were reported at the discretion of the investigator, thereby limiting the interpretability of the results. 1 SCT S and 2 placebo Ss had "clinically significant" ECGs involving bradycardia at endpoint. S7111 is described in subsection K who showed bradycardia, short PR interval and prolonged QT interval (QT of 456 msec, QTc Bazett's of 444 msec) on Day 57 of treatment. However, normal values were revealed one month later as treatment was continued. No associated AEs were reported in this S. However, this S discontinued study drug (one week into the extension trial) due to increased weight. Refer to subsection K below for details on ECG results which also show small treatment group effects on QT interval and HR, similar to that described in current Lexapro® labeling.

The GAD extension trial (Study MD-17) did not reveal any remarkable findings pertinent to cardiac conduction related effects, with the following possible exception. Section K describes S7110 who was in the extension GAD trial (Study MD-17) who had first degree AV block that may be drug-related. The event appeared to be mild, based on the PR interval (a copy of the ECG could not be found) and that the S did not appear to have associated AEs or other related clinical abnormalities. Yes, this event lead to treatment cessation and was previously described under subsection F of this review. First degree AV block was reportedly "confirmed" by a cardiologist 19 days after treatment, yet the PR interval was similar to baseline values (PR of only 211 msec) and no other data or a copy of the ECG could be found. Nevertheless, benign first degree AV Block is not uncommon in the healthy general population (i.e. athletes, the young).

In conclusion, one potential concern is regarding special populations at risk of bradycardia, conduction defect, and QT prolongation. This concern is further discussed in Section IXE on special populations, later in this review.

H. Adverse Events in the 8-Week GAD Trials (SCT-MD, -05,-06, and-07)

Table VII.H. 1 shows the incidence rates of common (≥5% of SCT Ss) AEs, as provided by the sponsor. The common AEs that occurred in at least twice the incidence in SCT Ss compared to the incidence in placebo Ss were generally similar to those observed in trials supporting the MDD indication and are listed in the following:

- Nausea
- Ejaculation Disorder
- Insomnia
- Fatigue
- Libido decreased

- Anorgasmia (in women)

Somnolence occurred in almost twice the incidence of SCT Ss (13.1%) compared to placebo (6.6%).

Dose-dependency of AEs was not examined as all the trials employed one dose level using a flexible dose design.

Subgroup Analyses of AE's on the Basis of Gender, Age-group or Race.

Sample sizes were not adequate to interpret results for treatment group effects on the basis of age (insufficient number of Ss over 60 years old) or ethnicity (the majority were Caucasian). Refer to subsection B above for the distribution of Ss by demographic features.

Possible gender differences may exist for some AEs, as described in the next paragraph and as shown in the table that follows. However, these results are only considered preliminary for several reasons. Firstly, the overall numerical trends between the treatment groups generally appear to be similar in male and female subgroups. Furthermore, a Type I error is a concern given that multiple comparisons are being made. Finally, a clinical basis for revealing a potential gender by treatment group effect for a given AE (shown in the table, below) is not apparent.

This paragraph describes the table below regarding potential gender differences on treatment group comparisons on the incidence of AEs. The table shows common AEs (AE with an incidence rate of >5% in either SCT group) that meet either of the two following criteria. One criterion is that the common AE must show an incidence rate in the SCT group in one gender that was at least twice that of the placebo group (in that same gender), while the AE does not show this pattern for a treatment group difference in the other gender. The other criterion is that the common AE must show a treatment group difference on the incidence rates in one gender that is at least twice the treatment group difference in the other gender. The table generated by each of these criteria, as shown below, does not include gender specific AEs (such as ejaculation disorder or anorgasmia). A section on gender specific AE's is already included in labeling. This section of labeling is updated in the sponsor's proposed labeling (in this submission) to incorporate data from the GAD trials.

Common AEs (>5%) Meeting Specified Criteria on Gender by Treatment Group Differences on Incidence Rates*

Preferred Term	Male		Female	
	Placebo (N=195) n (%)	Escitalopram N=182) n (%)	Placebo (N=232) n (%)	Escitalopram N=247) n (%)
Fatigue	6 (3.1)	11 (6.0)	3 (1.3)	22 (8.9)
Insomnia	9 (4.6)	15 (8.2)	15 (6.5)	36 (14.6)
Dry Mouth	9 (4.6)	18 (9.9)	14 (6.0)	20 (8.1)
Headache	32 (16.4)	36 (19.8)	39 (16.8)	65 (26.3)
Upper Respiratory Tract Infection	15 (7.7)	10 (5.5)	18 (7.8)	23 (9.3)
Diarrhea	9 (4.6)	17 (9.3)	16 (6.9)	19 (7.7)
Constipation	5 (2.6)	5 (2.7)	10 (4.3)	17 (6.9)
Libido decreased	5 (2.6)	15 (8.2)	4 (1.7)	14 (5.7)
Influenza-like symptoms	4 (2.1)	8 (4.4)	12 (5.2)	13 (5.3)
Sweating Increased	2 (1.0)	10 (5.5)	2 (0.9)	6 (2.4)

*AEs must meet either of the two following criteria to be shown in this table: a) must show an incidence rate in the SCT group that was twice that of placebo in one gender but did not meet this criterion in treatment groups of the other gender or, b) the treatment group difference on incidence rates in one gender must be at least twice that of the other gender.
Datasource: this table was derived from Panel 21 on page 40/42 of the ISS

I. Laboratory Findings

Laboratory assessments were conducted at baseline and treatment endpoint (week 8 of double-blind treatment) with results shown for the ITT safety population. No new or unexpected, remarkable findings were revealed.

1. Analysis of Central Tendency in Completed GAD Trials (SCT-MD-05, -06, and -07)
Hematology and Chemistry. Treatment groups were generally similar on mean baseline, mean change and range of change from baseline values of each parameter (results are provided in Table 6.4 in the ISS).

2. Analysis of Outliers in Completed GAD Trials (SCT-MD-05, -06, and –07)
Table VII.I.1 in the appendix shows outlier criteria employed for hematology, chemistry and urinalysis parameters (as provided by the sponsor).

Hematology. Treatment groups were generally similar on incidences rates of Ss meeting criteria for being potentially clinically significant (PCS) on various hematology parameters, as shown in the table below. The one exception is hemoglobin, but the incidence rate in SCT Ss is low. Furthermore, mean change in hematology parameters failed to show group differences. None of the Ss discontinued treatment as a result of meeting outlier criteria. One AE (0.2%) was anemia and was associated with a PCS hemoglobin value of 6.08 mmol/L (S5148). According to the narrative, this S completed trial MD-05 but her anemia continued and she did not enter into the extension trial (SCT-MD-17). In the absence of additional information, this event could have been drug-related. Anemia is listed as an infrequent AE in proposed labeling under "Other Events Observed During the Premarketing Evaluation of Lexapro" section.

Incidence of Subjects (%) Meeting PCS Criteria on Hematology Parameters*			
Hematology Parameter (units)	**PCS Criteria**	**Placebo**	**Escitalopram**
Hemoglobin (mmol/l)	≤0.9 LNL**	1/368 (0.3)	4/375 (0.8)
Eosinophils (%)	10	3/368 (0.8)	1/375 (0.3)
White Cell count (g/l)	≤2.8	0/368 (0)	1/375 (0.3)
* This table is similar to Panel 26 in the ISS and only shows parameters with at least one S meeting the outlier criterion for the given parameter. **LNL is lower normal limit of laboratory reference range			

Chemistry. Overall, treatment groups were generally similar on incidence of Ss meeting PCS criteria. The incidence rates were small. The maximum incidence rate in SCT Ss for any given parameter was 1.6% (elevated cholesterol) and in placebo Ss was 2.2% (for elevated cholesterol, as well). The table below only shows results of parameters with at least one SCT S meeting outlier criteria. None of the Ss in the 3 completed GAD trials discontinued treatment due to meeting outlier criteria or had an SAE of a parameter meeting outlier criteria. The following AEs were reported: hyperglycemia in S6234 and increased hepatic enzymes in S6034 but these Ss did not meet outlier criteria.

Incidence of Subjects (%) Meeting PCS Criteria on Chemistry Parameters*			
Chemistry Parameter (units)	**PCS Criteria**	**Placebo**	**Escitalopram**
ALT (SGPT) (U/l)	≥3*UNL	0/368	1/379 (0.3)
AST (SGOT) (U/l)	≥3*UNL	1/366 (0.3)	0/379
Blood Urea Nitrogen (mmol/l)	≥10.7	2/370 (0.5)	2/380 (0.5)
Cholesterol, Total (mmol/l)	≥7.8	8/370 (2.2)	6/380 (1.6)
Potassium (mmol/L)	≤3.0	1/369 (0.3)	1/379 (0.3)
	≥5.5	6/369 (1.6)	4/379 (1.1)
Total bilirubin (umol/l)	≥34.2	1/369 (0.3)	1/379 (0.3)
* This table is similar to Panel 27 in the ISS and only shows parameters with at least one S meeting the outlier criterion for the given parameter.			

As previously described S6155 had elevated LFTs as an ADO in the extension GAD trials, Study MD-17 (see subsection F).

Urinalysis.
Results were unremarkable with groups being generally similar.

J. Vital Signs and Body Weight in GAD Trials (MD-05, -06, and –07, combined).
Mean change from baseline to treatment endpoint and incidence of Ss in each treatment group that met outlier criteria on each parameter failed to show new, unexpected or remarkable findings. Refer to Tables VII.J.1-2 in the appendix for a summary of study results.

Similar to that previously observed in depression trials (refer to reviews under NDA 21-323 and NDA 21-440) and for the racemate, citalopram (refer to approved labeling), the incidence rates of outliers and mean change on heart rate shows a small effect on decreasing heart rate. However, the magnitude of this effect appears small. The mean decrease from baseline to endpoint on heart rate was only by 1.6 bpm in SCT Ss compared to a decrease of 0.7 bpm in placebo Ss.

The incidence rate for decreased pulse rate (defined as a pulse rate of ≤50 and a decrease ≥15 bpm) was 0.5% in SCT Ss compared to 0.2% in placebo Ss. Yet, no SCT Ss and 0.5% of placebo Ss showed an increased heart rate (defined as ≥120 bpm and increased by ≥15 bpm). These results suggest a small decrease in heart rate associated with SCT treatment.

None of the outliers on vital signs or weight measures were associated with SAEs resulted in an adverse dropout. However, one SAE (S7013) had an SAE of hypertension (not included in the incidence table of outliers; Table VII.J.2) in which her high reading was during hospitalization). This S was previously described under subsection E. A review of a line listing of outliers on decreased HR (Table A.2. in Appendix I of the ISS) failed to yield any remarkable findings for symptoms associated with the decreased HR (either by the type of AE reported or by the time that the AE was reported relative to the decreased HR). However, 2 Ss (S5049 and S5065) had baseline HRs in the 60s (in bpm) who showed a decrease in HR into the 40s (as low as 40 bpm), that were not reported as being associated with any AEs or other clinical abnormalities.[4]

[4] Outliers on decreased HR as described in the narratives: **S5049** in MD-05 (a 37 year old male with no medical history or concomitant medications described in the narrative) with baseline HR of 60 bpm decreased to 40, 44, and 44 on weeks 2, 4, and 6. HR was 50 bpm at the end of the study. No AEs "potentially related" to the decreased HR. The S completed the study and continued into the extension trial (MD-17). **S5065** (MD-05 page 77) was an ADO

K. Electrocardiographic Results

A DSI investigation for the original NDA 21-323 submission, revealed invalid ECGs in studies that supported the depression indication. The invalid ECGs in these earlier depression trials, occurred in Ss at study sites using the [ ] device, in which the EKG assessments were conducted at a central ECG Laboratory [ ] Therefore, the sponsor was inquired about ECG data in the GAD trials. In the sponsor's 1/7/03 response, they indicated that none of the sites of the GAD trials (MD-05, -06 and –07) used this central laboratory that used the [ ] device, as the ECGs in GAD trials were done locally. However, the sponsor is confirming this by contacting the study sites and will notify the Agency "in the event of any updates." At the time of this writing the sponsor has not submitted any reports of the invalid EKGs, subsequent to the sponsor's 1/7/03 amendment submission in response to our inquiry. As a final note, Dr. Ni Khin (from DSI) verified that the following study sites used the above central laboratory and/or [ ] devices: sites SCT-MD-01, 2 and 4 (as conveyed during the 1/13/03 filing meeting for this sNDA). These sites are not among the GAD trials of the current SE1-003 submission.

K.1 Analysis of Central Tendency

Completed 8-Week GAD Trials (SCT-MD-05, -06, and -07)

The table below shows the descriptive statistical ECG results. These results generally appear to be similar to results from the pivotal MDD trials that were conducted to support the MDD indication (PR interval results not provided). These earlier results from the MDD trials are shown in Table 2 in section 2.2 of Dr. David Ghan's Safety Group review dated 8/12/02 (which excludes data from invalid ECGs revealed by DSI in MDD trials). For the convenience of the reader, a copy of Dr. Ghan's Table 2 is also provided in Attachment 1 of this review.

Mean Change from Baseline to Treatment Endpoint on ECG Parameters in Each Treatment Group		
ECG Parameter:	**Placebo (N*=373)**	**SCT (N*=381)**
Ventricular Heart Rate (bpm)	1.2	0.1
PR Interval (msec)	-0.6	0.4
QT Interval (msec)	-4.2	1.8
QTc Bazett's Interval (msec)**	-1.1	2.9
QTc Fridericia Interval (msec)**	-2.2	2.6
*The number of treated SS with both screening and at least one post-baseline ECG assessment ** Bazett's correction = QT interval/(60/heart rate)$^{1/2}$, Fridericia's correction=QT interval/(60/heart rate)$^{1/3}$		

While there appeared to be some numerical trends for greater mean changes in QT or QTc intervals, PR interval, as well as for ventricular rate in the active treatment groups compared to the placebo group, these group differences were small. Treatment groups were also generally similar on results on the median and range on each of the above ECG parameters.

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due to nausea and metallic taste in the her mouth but also an outlier on decreased HR. Her HR decreased to 48 bpm at week 2 of treatment (study drug discontinued on Day 19 of treatment) from a baseline HR of 68 bpm. She had no AEs that appeared to be associated with a reduced HR.

K.2 Analysis of Outliers

Completed 8-Week GAD Trials (SCT-MD-05, -06, and -07)

The following table shows results of outliers on prolong PR or QTc intervals.

The Incidence of Outliers on ECG Parameters in Each Treatment Group			
ECG Parameter:	**Outlier Criteria**	**Placebo (n/N)**	**SCT (N=n/N)**
PR Interval (msec)	≥250	0/371	2/381 (0.5%)
QTc Bazett's Interval (msec)**	>500	0/373	0/381
*The number of treated SS with both screening and at least one post-baseline ECG assessment ** Bazett's correction = QT interval/(60/heart rate)$^{1/2}$, Fridericia's correction=QT interval/(60/heart rate)$^{1/3}$			

Outliers on increased PR interval (2 SCT Ss) did not have any AEs that appeared to be cardiac related (one had ejaculation disorder as an AE which is a known AE associated with SSRIs). None of AEs, ADO or SAE in the 3 GAD trials were due to an ECG parameter meeting outlier criteria. One SCT S (0.2%) and 3 placebo Ss (0.7%) had the AE of "abnormal ECG" (identified as such by the investigator).

The sponsor also describes ECGs reported as "clinically significant" according to the discretion of the investigator in the 3 completed GAD trials. 1 SCT S and 4 Placebo Ss had "clinically significant" ECGs. The SCT S (S7111) had an abnormal ECG at baseline (not considered clinically significant) and had sinus bradycardia with a short PR interval at treatment endpoint (after completing 57 days of SCT in study MD-07). This S discontinued the study drug one week later in the open label SCT extension study (MD-17) due to increased weight and was previously described under subsection F under ADOs. However, upon request for additional ECG and AE information, QT prolongation was also found to be observed at treatment endpoints, according to ECG values reported in a 3/20/03 amendment submission. The QT interval was 456 msec and HR was 57 bpm on Day 57 of treatment compared to a QT interval of 428 msec and HR of 61 at baseline. QTc (Bazett's) on Day 57 was 444 msec. While this event could be drug-related a repeat ECG (approximately one month later) during treatment revealed normal values (QT of 424 msec, HR of 70 bpm) that were similar to values at baseline and at one week after treatment cessation. This S also appeared to have no AEs, associated with this event. A small decrease in heart rate is not unexpected for SCT. Increased QT interval can be influenced by changes in HR and with Bazett's correction the QTc interval was under 450 msec. No SAEs or ADOs due to prolongation of QT or bradycardia in the 3 completed GAD trials or in the ongoing extension GAD trial (MD-17).

While a number of Ss were reported as having ECG abnormalities in the 3 GAD trials, the type of abnormality was not recorded since they were considered by investigator as not being clinically significant.

The following abnormal ECG reading results in an ADO was described in the ongoing extension trial SCT-MD-17. The SCT S (#7110) discontinued study drug due to a first degree AV block (PR interval of up to 220 during treatment that resolved after treatment cessation and 19 days after treatment cessation). This S was previously described under subsection F on ADOs. The temporal relationship of prolongation of the PR interval (up to 220 msec) with study drug is suspicious of being drug-related. However, it is possible that the S had a pre-existing or benign condition, for reasons previously described above (under subsection F).

L. Overdose Experience

The sponsor reports a total of 2 overdoses (ODs) with SCT in clinical trials and a 3rd overdose in the child of a S in clinical trial (that were reported between the cut-off dates of 12/2/0/1 and 7/1/02). The sponsor did not report any new information on events associated with OD and that are not already described in the "Overdosage" section of approved labeling. While actual results of diagnostic tests were not provided on the 3 ODs, two of ODs were treated immediately by gastric lavage (no AEs were described by the sponsor). The third OD (S8055 who experienced impaired consciousness requiring intubation, incoherent but positive gag reflex) had ingested multiple drugs (SCT, fluoxetine and acetaminophen). Coma is already described in approved labeling. Proposed labeling includes a change in the total number of Ss who ODed from 3 Ss to 5 Ss in the "Overdosage" section of proposed labeling.[5] [redacted]

[redacted]

M. Safety Results from Other Sources

Literature: A total of 35 published articles were found using search methods described in Section IV.D of this review. According to the sponsor none of these articles provided new safety information on SCT or on citalopram (the racemate of SCT).

Post Marketing Reports: Section IV.C. of this review describes the post-marketing experience with SCT. Among 12,700 treated patients in 8 countries where SCT is approved for marketing only one SAE is reported (between 1/1/02 and 7/1/02). This SAE (Mfr report #S02-SWI-00915-01) was suicide by hanging in a patients receiving 10 mg of daily SCT, 3 mg/day of bromazepam and somnium (1 tablet/day). This SAE is most likely reflecting underlying psychopathology and lack of efficacy of the patient's treatment. MedWatch report in Appx X (as cited on page 62/64 of ISS).

N. Safety Information on Pregnancy.

The sponsor provides some information on pregnancy as described in this section. This information is only considered preliminary and is not adequate for making conclusions regarding potential effects of SCT on pregnancy. Only a few pregnancies occurred and cannot be differentiated form the background rates for pregnancies and miscarriages. Furthermore, studies were not designed to specifically examine potential effects. The following are reported pregnancies in clinical trials and provides observations (as described in section 19.0 of the ISS on page 65 in the submission):

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[5] **S7187** in the extension GAD trial (MD-17) ingested 38 10 mg tablets of SCT (380 mg total) on impulse after a spousal argument. She "immediately" called 911, and had her "stomach pumped" in the emergency room and recovered. She withdrew from the study due to this SAE.
S8055 in a multi-phase "prevention of depression recurrence" trial (MD-11) took an intentional overdose (OD) of blinded study drug (20 mg SCT tablets) and concomitant medications (fluoxetine and acetaminophen). The actual amount of each drug ingested was not specified in the narrative. The S underwent gastric lavage (recovered gastric were the above three drugs). The S was unresponsive to stimuli, incoherent, but had a positive gag reflex (Glasgow Coma Scale score was 9) and was hospitalized. The following treatment was given: intubated/oxygenated, given etomidate and succinalcholine, for agitation after intubation the S received Vecuronium, morphine and midazolam. The S "recovered" but was transferred to another hospital for "insurance reasons." The S was in Study MD-11 for almost 1 ½ years and received the following prior to the OD: 56 days of citalopram, then 112 days of SCT in the open label phases, then 336 of double-bind SCT (20 mg/day).
The child of S6004 in Study MD-19 overdosed on the patient's study drug. The child was treated with gastric lavage and activated charcoal in the emergency room and had no AEs.

- Completed GAD trials (MD-05, -06, -07):
  - S 6201 who delivered a "healthy baby girl"
- Ongoing Extension GAD trial (MD-17):
  - S6147-had a miscarriage "possibly related to study medication"
  - S6272
  - S7255
- Study SCT-MD-11:
  - grossly S8517-delivered by C-section. The relationship of the study drug appeared to be unlikely for several reasons. Complications were associated with the and occurred at 39 weeks (approximately 10 months), approximately 10 months after drug exposure (mother was found to be pregnant by urine testing in the study and stopped study drug immediately). Furthermore, no malformations or abnormalities were observed in the baby and the mother and baby were discharged within 4 days after labor induction was first initiated. [6]
  - Study 99269
  - One S (S# not provided)-study drug is still blinded
- Study 99270
  - 3 Ss (S #s not provided -study drug is still blinded

No other information can be found, other than a narrative for S8517.

O. Conclusions on Safety Results.

Overall safety results appear to show that SCT is adequately safe for treatment of patients with GAD. Several safety issues impacting on recommendations for labeling are discussed in other sections of this review (primarily in Section IX on Specific populations, and Section X Conclusions and Recommendations).

One potential safety issue not addressed in other sections of this review, is the possible association between SSRI treatment and upper gastrointestinal bleeding, as suggested in an epidemiological study described in the literature, de Abajo, et al., 1999, also refer to section IC of this review). The safety results described by the sponsor fail to show evidence for an association of SCT with upper GI bleed or with hemorrhage. This conclusion is based on laboratory and safety analysis, as well as upon examination of incidence rates of common AEs in the four 8-week depression trials by use of anti-inflammatory and anti-rheumatic products or by use of analgesics. One S (S2374) had an SAE of "stomach ulcer and hemorrhage" who was not taking a non-steroidal anti-inflammatory agent. This S had a positive history of peptic ulcer disease. The other SCT S (3188) had alcohol abuse disorder and was believed to have been actively consuming alcohol whereby he had a series of events associated with the gastrointestinal (GI) system that included the SAEs of gastritis and hematemesis. These 2 Ss were the only Ss with SAEs involving upper GI bleed out of 2552 SCT Ss and 816 CT Ss. It is also noted that 1 placebo S out of 1199 placebo Ss who had a SAE of gastric ulcer. Consequently, the possible

[6] S8517 had a positive urine pregnancy test on [redacted] during participation of MD-11 after approximately 2 months of 10 mg SCT administered daily. The S withdrew from the study. On [redacted] labor was induced (Pitrocin i.v.) due to a history of pelvic pain and persistent contractions (at 39 week gestation). The S underwent C-section (Pitrocin was decreased and eventually discontinued due to poor quality of contractions, no change in cervical dilatation and "non-reassuring fetal heart patterns"). Upon delivery, the baby had no observable malformations or abnormalities and the mother and baby were discharged on [redacted].

association of the SSRI, SCT and upper GI bleeding is not supported by the safety findings described in the submission. Refer to Section IC above regarding a further discussion of this topic, as it pertains to the class of SSRIs.

VIII. Dosing, Regimen and Administration Issues

A. Initial Treatment.

The proposed direction for use of Lexapro™ for GAD is similar to that for the previous approved indication, MDD. As with MDD the sponsor proposes the recommendation of 10 mg daily as the starting dose (may be given with or without food and in the evening or the morning). Additionally the proposed labeling indicates that the [redacted]

Since the GAD trials involved a flexible dose regimen, the sponsor did not examine dose-dependent effects of SCT (e.g. between 10 mg and 20 mg dose levels). However, results on exposure as follows, suggest that a number of Ss remained within the 10 mg dose level during the study. The mean daily exposure among SCT treated Ss in the ITT Safety population was approximately 13 mg (mean daily dose in completers was approximately 13 mg, ranging from approximately 9 to 18 mg, daily). Approximately 37% of SCT Ss in the ITT Safety population received a mean daily dose of 6 to 10 mg of SCT (for any given duration) and 25% of the SCT Ss (of the ITT Safety population) received at least 56 days within this daily dose-range (6-10 mg).

B. Maintenance Treatment.

The GAD trials were short term trials and the sponsor does not provide any data on longterm or maintenance treatment. Refer to Section XB below describing a recommendation pertinent to this aspect of the sponsor's proposed labeling.

IX. Use in Special Populations

A. The Elderly Population

The sample size of elderly Ss was insufficient in the GAD trials from which to derive any new or definitive information other than that described in approved labeling. Proposed labeling does not contain any revisions of sections pertinent to the elderly population or a change in the recommended dose administration.

B. Patients with Impaired Renal or Hepatic Function

No new information is provided in this sNDA submission.

C. Male and Female Populations

Section VII H describes potential gender differences in the incidence of AEs (by preferred term) that are not included in proposed labeling. Refer to Section X for recommendations. No gender effects were reported on the primary efficacy variable.

D. Ethnic Populations

Ss were primarily Caucasian and the sample size of each of the other ethnic subgroups was insufficient to conduct a subgroup analysis on the basis of ethnicity for each study.

E. Other Special Populations.

This section focuses on concerns described in previous reviews by this reviewer on escitalopram regarding the safety results on decreased heart rate and various ECG observations. The Division Safety Group reviewed the sponsor's submissions and recommended approval of Lexapro™ (NDAs 21-323, 21-365 and 21-440) and provided recommendations for labeling (as appears in currently approved labeling). More recently, the sponsor submitted a post-approval submission under submission under NDA 21-323, dated 11/12/02 providing additional information on SCT and QT data in one of the MDD trials (MD-01), in response that requested in the 8/14/02 approval letter (the Division desired this additional information). A copy of the conclusion and recommendation section of the review of this submission is provided in Attachment 2. This review also summarized results of a 9/30/02 ODS consultative review that was conducted upon a request by the Safety Group. The ODS consultant concluded the following after conducting an analysis of postmarketing citalopram data and conducting a review of the literature:

It would be prudent to advise caution in prescribing citalopram to patients with risk factors for developing QT prolongation and ventricular arrhythmia

[ ]

The Safety Group is conducting a consultative review at the time of this writing, as recommended in the above-mentioned Clinical review of the 11/12/02 NDA 21-323 response submission and in light of the above ODS recommendation (refer to Attachment 2 for details).

This of paragraph summarizes previously expressed cardiac-related concerns in special populations, as described in earlier reviews under this NDA. For more details on these concerns refer to previous reviews under NDAs 21-323, 21-365 (the oral solution), 21-440 (for longer term treatment of MDD) and a review of a post-approval submission under NDA 21-323, dated 11/12/02. In summary these reviews discussed potential safety concerns regarding one special patient population, patients with existing bradycardia, or with a pre-existing conduction defect or patients that are at risk for developing a conduction defect. A small mean decrease in heart rate and QT or QTc prolongation appears to be reproducible in clinical trials and in various patient populations (healthy Ss, patients with MDD, and in the current submission in patients with GAD). Refer to Section VII for more details on observations pertinent to heart rate and ECG observations in the GAD trials. As described in previous reviews three PK studies (described in the original NDA submission) had multiple ECG assessments that included assessments conducted at approximately Tmax. These more controlled, but small studies, also revealed at least trends for bradycardia and Ss meeting outlier criteria for bradycardia. Furthermore, several Ss had first degree heart block in both the PK trials and the MDD trials submitted in the original NDA21-323. It was previously noted that Ss meeting PCS for bradycardia (in the PK trials) tended to have HRs in the low normal range at baseline (approximately 64 to 76 bpm) such that patients with low normal HRs or bradycardia at baseline appear to be at greater risk of bradycardia during SCT treatment.

Also described in previous reviews under this NDA, are reports in the literature (Nyth et al, 1992, Nyth & Gottries, 1990) of possible worsening of bradycardia in elderly depressed patients with or without dementia or in patients with psychopathology associated with dementia being treated with CT. One case reported in the literature involved a patient who required a temporary pacemaker until the bradycardia resolved (refer to previous reviews by this author under NDA 21-323 for details and a reference).

Given these observations and observations described in the current review, caution may be needed regarding SCT treatment in patients with existing bradycardia, or a conduction defect or for patients that are at risk for conduction defect. One must consider the possibility that an exacerbation or development of bradycardia and other possible sequelae, such as an arrhythmia may occur with SCT treatment in this special patient population.

The magnitude of a potential effect of SCT on the following EKG parameters was small: prolonged QT interval, prolonged PR interval, decreasing HR or increasing incidence of bradycardia. Therefore, these results do not appear to be of clinical significance for the generally healthy patient who does not have cardiac-related risk factors. A precautionary statement is recommended for labeling regarding patients with pre-existing bradycardia, conduction defects or arrhythmias before considering SCT treatment. Similarly, [ ] Refer to previous reviews by this author under this NDA for further details and recommendations.

X. Conclusions and Recommendations

A. Conclusions

Three (MD-05, -06, and -07) of the three studies showed significant treatment group effects on efficacy in favor of SCT treatment based on the sponsor's results as described in the submission (pending confirmation by Biometrics). However, the Biometric Reviewer, Dr. Kun He, revealed the following issues. Dr. He noted that 8 out of 25 sites in Study-05 and 6 out of 19 sites in Study-06 had negative results (the placebo group showed numerically greater mean improvement than the SCT group on the primary efficacy variable). An additional site in Study-06 showed similar efficacy results in the placebo and SCT groups (no treatment effect). Furthermore, the site with the greatest treatment group difference on the primary efficacy variable for a given study (the outlier site) was in the positive direction (in favor of SCT over placebo) and that the mean treatment group difference was greater than two standard deviations from the treatment group difference mean for the trial (all sites combined). Each of these outlier sites had a mean treatment group difference that was large enough to skew the overall results in the positive direction for two of the three trials (Studies MD-05 and -06), based on the following. Dr. He reanalyzed the efficacy data of each trial, deleting data from the outlier site of the given trial and revealed that Studies MD-05 and-06 were no longer positive (i.e. no longer showed significant treatment group effects with $p=0.06$ and $p=0.15$, respectively). However, Study MD-07 remained positive (i.e. showed significant treatment group effects with $p<0.0001$). It is not clear why an unusually large proportion of study sites in Studies-05 and-06 showed greater improvement in placebo compared to SCT treatment groups within each of these sites and why the outlier sites were markedly positive skewing the overall results in two of the three trials (enough to make overall study results show significantly positive effects of SCT over placebo). Therefore, DSI is being consulted regarding this concern, and will be conducting study site visits at two sites (the outlier sites identified by Dr. He in Studies -05 and-06).

Regarding the overall safety of SCT in GAD patients, SCT treatment appears to be adequately safe in this population. The safety profile generally appears to be similar to that observed in previous SCT trials described in previous submissions under this NDA, as well as, for other SSRIs and/or for CT. See labeling recommendations below (subsection B) regarding cardiac-related concerns and special populations, and other recommendations.

One area regarding safety that is not addressed in other sections of this review, is regarding potential discontinuation effects of SCT, as with other selective serotonin reuptake inhibitors. Refer to previous reviews of submissions under NDA 21-323 for further details. The safety results described in the current supplemental NDA submission did not reveal evidence for AEs associated with discontinuation of SCT treatment. However, the potential safety issue of withdrawal-like effects with CT or SCT has not been systematically investigated. Therefore, consideration may be given to examining postmarketing reports of AEs associated with cessation of treatment regarding this class of drugs, the SSRIs, similar to that described in the labeling of other SRRIs. Alternatively, the sponsor may wish to conduct well designed controlled studies that provide evidence refuting the possibility for withdrawal effects associated with abrupt cessation of paroxetine treatment. This SRRI drug class issue is currently under review by the Psychiatry Drug Products Group in the Division.

The issue of abnormal bleeding associated with SSRIs was previously discussed in this review and is a topic under review by that Safety Group in the Division.

B Recommendations

From a clinical perspective, it is recommended that the supplemental NDA be granted an approvable status. However, it is recommended that before consideration is given to ultimately approving this submission, that the following issues be resolved:

- That the DSI investigation reveals no remarkable findings that would impact on the interpretation of the results of the studies (including the efficacy data from outlier sites of Studies-05 and-06, as previously discussed in subsection A, above).
- That the Biometric reviewer is able to resolve biometric-related concerns and can confirm that at least two out of the three studies are positive for an SCT effect on GAD (as previously discussed in subsection A, above).

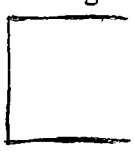
At the time of this writing, CMC review is pending, but the CMC reviewer has not conveyed any major issues.

SCT appears to be adequately safe within the proposed dose range for the generally healthy patient population with GAD.

Given that the above concerns can be resolved, some major labeling recommendations that are not previously discussed in other sections of this review, are described below.

Labeling.

Proposed labeling changes generally appear to be acceptable to this reviewer, as long as the above issues can be resolved. However, some exceptions are described in the following that are either not discussed elsewhere in this review or are considered by this reviewer as key labeling issues.



Safety related recommendations for labeling:

- Sections VII and IX of this review, discuss cardiac-related concerns with a recommendation for describing these concerns regarding special populations at risk for the observed cardiac-related events (bradycardia, QT interval prolongation and other potentially related conduction defects). [redacted]

  Refer to previous sections of this review for details.
- Potential gender group differences on the incidence of AE's are described in this review under section VII H. Consideration should be given to including results described in this section in labeling under "Adverse Reactions."
- S1532 (in blinded study 99269) was reported as having a seizure. The subject was a 28 year old female with a history of a seizure at 6 years old. Labeling already includes a precautionary statement regarding patients with a history of seizures. In a 3/12/03-amendment submission that included some updated information, the study drug in S1532 was unblinded and found to be SCT. It is recommended that this subject is counted among subjects having seizures, as described under the "Precautions" section of labeling.
- S1184 (panel 16 in the ISS) had hypomania on blinded drug (in Study 99269). This subject was described in a later amendment submission as having received SCT. Therefore, the section on mania under "Precautions" should be updated to include this S in the enumeration of subjects of seizures.
- [redacted]

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
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APPENDIX

Table VI.B.1 Investigator Information

SCT-MD-05 Investigator List

Site Number	*Investigator*	*Phone / Fax*
01	**Jay Amsterdam, MD** University of Pennsylvania Depression Research Unit - 8th Floor 3600 Market Street Philadelphia, PA 19104-2649	*Phone:* 215-662-3462/ 215-662-6704 *Fax:* 215-662-6443
03	**John Carman, MD** 4015 S. Cobb Drive Suite 245 Smyrna, GA 30080	*Phone:* 770-333-0093 *Fax:* 770-432-2643
04	**Evagelos Coskinas, MD** Affiliated Research Institute 801 N. Tustin Avenue Suite 600 Santa Ana, CA 92705	*Phone:* 714-972-0172 *Fax:* 714-835-9493
05	**Lynn Crismon, PharmD** Center for Clinical Research-Austin 12221 MoPac Expressway North Austin, TX 78758	*Phone:* 512-901-4500 *Fax:* 512-901-3980
06	**Joseph David, MD** Charlottesville Medical Research 1139 E. High Street Suite 105 Charlottesville, VA 22902	*Phone:* 804-817-8484 *Fax:* 804-817-8492
07	**Jonathan Davidson, MD** Duke University Medical Center Box 3812 Durham, NC 27710	*Phone:* 919-684-2880 *Fax:* 919-684-8866
08	**Naresh P. Emmanuel, MD** Clinical Research Associates Department of Psychiatry 712 Richland Street, Suite J Columbia, SC 29201	*Phone:* 803-253-4005 *Fax:* 803-253-4197
09	**James M. Ferguson, MD** Pharmacology Research Clinic 448 East 6400 South Suite 200 Salt Lake City, UT 84107	*Phone:* 801-261-8930 *Fax:* 801-261-0445

Table VI.B.1 Investigator Information

SCT-MD-05 Investigator List

Site Number	*Investigator*	*Phone / Fax*
10	**K. Wayne Goodman, MD** University of Florida Behavioral Health Clinic Mandarin 2970 Hartley Road, Suite 202 Jacksonville, FL 32257	*Phone:* 904-292-2773 *Fax:* 904-292-1747
11	**Howard A. Hassman, DO** Comprehensive Clinical Research, Inc. 130 White Horse Pike Clementon, NJ 08021	*Phone:* 856-566-9000 *Fax:* 856-566-9701
12	**Jon Franklin Heiser, MD** 1601 Dove Street Suite 290 Newport Beach, CA 92660-2814	*Phone:* 562-795-9175/ 949-752-7910 *Fax:* 562-795-6935/ 949-752-1412
13	**Peter Holland, MD** Boca Raton Medical Research, Inc./Summit Research 7284 West Palmetto Park Road Suite 205-South Boca Raton, FL 33433	*Phone:* 561-368-8965 *Fax:* 561-368-6207
14	**Anita Kablinger, MD** LSU Medical Center Shreveport Department of Psychiatry, Room 3-412 Psychopharmacology Research Clinic 1501 Kings Highway, PO Box 33932 Shreveport, LA 71130	*Phone:* 318-675-6326 *Fax:* 318-675-4698
15	**Jeffrey Kelsey, MD, PhD** Emory University Department of Psychiatry & Behavioral Sciences 1841 Clifton Road, NE 4th Floor Atlanta, GA 30329	*Phone:* 404-727-3714 *Fax:* 404-727-3700
16	**Arif Khan, MD** Northwest Clinical Research Center 1900 116th Avenue NE Suite 112 Bellevue, WA 98004	*Phone:* 425-453-0404 *Fax:* 425-453-1033

Table VI.B.1 Investigator Information

SCT-MD-05 Investigator List

Site Number	*Investigator*	*Phone / Fax*
17	**Louis Kirby, MD** Pivotal Research Centers 13128 N. 94th Drive Suite Peoria, AZ 85381	*Phone:* 623-815-9714 *Fax:* 623-815-9759
18	**Susan Kornstein, MD** Virginia Commonwealth University Mood Disorder Institute 700 West Grace Street, Suite 303 Richmond, VA 23220	*Phone:* 804-828-5637 *Fax:* 804-828-5644
19	**Matig Mavissakalian, MD** Anxiety Disorders Program University Hospital of Cleveland 11100 Euclid Avenue Cleveland, OH 44106	*Phone:* 216-844-7156 *Fax:* 216-844-5177
20	**Mark Rapaport, MD** University of California, San Diego Department of Psychiatry 8950 Villa La Jolla Drive-Suite 2243 La Jolla, CA 92037	*Phone:* 858-622-6160 *Fax:* 858-450-1491
21	**Jeffrey Rausch, MD** Medical College of Georgia Outpatients Psychiatry 1515 Pope Avenue Augusta, GA 30912	*Phone:* 706-721-7793 *Fax:* 706-721-7796
22	**Robert Riesenberg, MD** Atlanta Center for Medical Research 811 Juniper Street Atlanta, GA 30308	*Phone:* 404-292-2000 *Fax:* 404-294-5919
23	**Murray H. Rosenthal, MD** Behavioral & Medical Research, LLC 3625 Ruffin Road, Suite 100 San Diego, CA 92123	*Phone:* *Fax:*
24	**Jeffrey Simon, MD** Northbrooke Research Center 9275 North 49th Street, Suite 200 Brown Deer, WI 53223	*Phone:* 414 357-9444 *Fax:* 414 357-9422

Table VI.B.1 Investigator Information

SCT-MD-05 Investigator List

Site Number	*Investigator*	*Phone / Fax*
25	**Lawson Wulsin, MD** Psychiatric Professional Services, Inc. 231 Bethesda Avenue, Suite 711 Cincinnati, OH 45267-0559	*Phone:* 513-558-3517/ 513-558-5192 *Fax:* 513-558-2661
26	**Charles Merideth, MD** Affiliated Research Institute 8880 Rio San Diego Drive Suite 1090 San Diego, CA 92108	*Phone:* 619-688-6565 *Fax:* 619-688-6569

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Table VI.B.2 Investigator Information

SCT-MD-06 Investigator List

Site Number	*Investigator*	*Phone / Fax*
01	**David Adson, MD** University of Minnesota Department of Psychiatry F282 / 2A West Building 2450 Riverside Avenue Minneapolis, MN 55454	**Phone:** (612) 273-9835 **Fax:** (612) 627-4808
03	**Robert Bielski, MD** Summit Research Network (Michigan), Inc. 23700 Orchard Lake Rd. Suite M Farmington Hills, MI 48336	**Phone:** (517) 349-5525 **Fax:** (517) 349-1046
04	**David W. Brown, MD** Community Clinical Research, Inc. 4411 Medical Parkway Austin, TX 78756	**Phone:** (512) 323-2622 ext:0 **Fax:** (512) 323-2625
05	**William Burke, MD** Department of Psychiatry 985581 Nebraska Medical Center Omaha, NE 68198-5581	**Phone:** (402) 354-6868 **Fax:** (402) 354-6896
06	**Ronald R. Fieve, MD** Fieve Clinical Services, Inc. 226 East 79th Street Ground Floor New York, NY 10021	**Phone:** (212) 772-3570 **Fax:** (212) 772-3550
07	**Howard A. Hassman, DO** Comprehensive Clinical Research, Inc. 130 White Horse Pike Suite B Clementon, NJ 08021	**Phone:** (856) 566-9000 **Fax:** (856) 566-9701
08	**Peter Holland, MD** Summit Research Network (Florida)/Boca Raton Medical Research Inc. 7284 West Palmetto Park Road Suite 205, South Plaza Boca Raton, FL 33433	**Phone:** (561) 368-8965 **Fax:** (561) 368-6207
09	**James Jefferson, MD** Rogers Memorial Hospital - Milwaukee 11101 W. Lincoln Avenue West Allis, WI 53227	**Phone:** 414 328-3791 **Fax:** 414-328-3721

Table VI.B.2 Investigator Information

SCT-MD-06 Investigator List

Site Number	*Investigator*	*Phone / Fax*
10	**Elly Lee, MD** Irvine Center for Clinical Research 16259 Laguna Canyon Road Irvine, CA 92618	**Phone:** (949) 753-1663 **Fax:** (949) 753-4761
11	**Ira M. Lesser, MD** Harbor-UCLA Research and Education Institute Department of Psychiatry 1124 West Carson Street Building F9 Torrance, CA 90502	**Phone:** (310) 222-3137 **Fax:** (310) 328-5546
12	**Dennis J. Munjack, MD** 435 North Bedford Drive Suite 216 Beverly Hills, CA 90210	**Phone:** (310) 858-7448 **Fax:** (310) 858-7489
13	**Murray Rosenthal, DO** Behavioral and Medical Research, LLC 1000 South Anaheim Blvd. Suite 204 Anaheim, CA 92805	**Phone:** 714-774-4800 **Fax:** 714-774-4840
14	**Jeffrey Ross, MD** Chicago Center for Clinical Research 515 N. State Street Suite 2700 Chicago, IL 60610	**Phone:** (312) 494-2227; 312-494-6206 **Fax:** (312) 494-6297
15	**Ward Smith, MD** Pacific Northwest Clinical Research 1849 N W Kearney Suite 201 Portland, OR 97209	**Phone:** (503) 279-8252 ext: 229 **Fax:** (503) 279-8926
16	**Richard Templeton, MD** ANPR Research, Inc. 108 Annapolis Street Annapolis, MD 21401	**Phone:** 410-263-4366 **Fax:** 410-268-5597
17	**Amit Vijapura, MD** Clinical Neuroscience Solutions, Inc. 4130 Salisbury Road Suite 2600 Jacksonville, FL 32216	**Phone:** 904-281-5757 **Fax:** 904-281-5758

Table VI.B.2 Investigator Information

SCT-MD-06 Investigator List

Site Number	*Investigator*	*Phone / Fax*
18	**Dan L. Zimbroff, MD** Pacific Clinical Research 100 S. Vincent Avenue, #405 West Covina, CA 91790	**Phone:** (909) 890-9400 **Fax:** (909) 890-9420
19	**Michael DePriest, MD** Protocare Trials Las Vegas Center for Clinical Research 6039 Eldora Avenue, Suite H	**Phone:** (702) 257-2600 **Fax:** (702) 227-1861
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Table VI.B.3 Investigator Information

SCT-MD-07 Investigator List

Site Number	*Investigator*	*Phone / Fax*
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03	**Bijan Bastani, MD** North Coast Clinical Trials Inc. 3733 Park East, Suite 100 Beachwood, OH 44122	**Phone::** (216) 514-1803 **Fax:** (216) 514-9241
04	**Alexander Bystritsky, MD** Valley Internal Medicine and Nephrology Medical Group 15211 Van Owen Blvd.; Suite 300 Van Nuys, CA 91405	**Phone::** Main: (310) 825-4321 Direct: (310) 206-5133 **Fax:** 512-323-2625
05	**Andrew Cutler, MD** Coordinated Research of Florida, Inc. 807 W. Morse Boulevard, Suite 801 Winter Park, FL 32789	**Phone::** 407-741-5811 **Fax:** 407-647-8103
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Table VI.B.3 Investigator Information

SCT-MD-07 Investigator List

Site Number	*Investigator*	*Phone / Fax*
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11	**James Ferguson, MD** Pharmacology Research Clinic 448 East 6400 South, Suite 200 Salt Lake City, UT 84107	**Phone::** 801-261-8930 **Fax:** 801-261-0445
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13	**Susanna Goldstein, MD** Medical and Behavioral Research, PC 65 Central Park West, Suite 1BR New York, NY 10023	**Phone::** (212) 362-6657 **Fax:** (212) 874-3129
14	**Ari Kiev, MD** Life Span Developmental Systems 150 East 69th Street New York, NY 10021	**Phone::** 212-249-6829 **Fax:** (212) 249-8546
15	**Michael Lesem, MD** Claghorn-Lesem Research, Inc. 6750 West Loop South, Suite 1050 Bellaire, TX 77401	**Phone::** (713) 665-6446 **Fax:** (713) 665-8796

Table VI.B.3 Investigator Information

SCT-MD-07 Investigator List

Site Number	*Investigator*	*Phone / Fax*
16	**Peter Londborg, MD** Seattle Clinical Research Center, Inc. 901 Boren Ave, Suite 1800 Seattle, WA 98104	**Phone::** 206-624-4587 **Fax:** 206-624-6975
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18	**Ronald D. Serota, MD** Jefferson Medical College Department of Psychiatry 833 Chestnut Street, Suite 210 E Philadelphia, PA 19107	**Phone::** (215) 955-2542 **Fax:** (215) 503-2850
19	**Kenneth Sokolski, MD** Advanced Behavior Research Institute 1735 W. Romneya Drive Anaheim, CA 92801	**Phone::** (714) 776-6176 **Fax:** (714) 774-7451
20	**Harold D. Udelman, MD** Biomedical Stress Research Foundation 45 E. Osborn Road Phoenix, AZ 85012	**Phone::** (602) 265-9051 **Fax:** (602) 266-9358
21	**Arif Khan, MD** Northwest Clinical Research Center 1900 116 Avenue NE, Suite 112 Bellevue, WA 98004	**Phone::** 425-453-0404 **Fax:** 425-453-1033
22	**Janice Miller, MD** CNS Healthcare 5601 Corporate Way Bldg. 2, Suite 210 West Palm Beach, FL 33407	**Phone::** (561) 616-9595 **Fax:** (561) 616-9545

Table VI.B.3 Investigator Information

SCT-MD-07 Investigator List

Site Number	*Investigator*	*Phone / Fax*
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25	**Amit Vijapura, MD** Clinical Neuroscience Solutions, Inc. 4130 Salisbury Road Suite 2600 Jacksonville, FL 32216	**Phone::** 904-281-5757 **Fax:** 904-281-5758

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Table VI.B.4 Schedule of Evaluations for Each of the 3 GAD Trials (Studies MD-05, -06 and –07)

			Double-Blind Treatment: End of Week				
Visit Name	*Screen*	*Baseline*	*1*	*2*	*4*	*6*	*8**
Visit Number	*1*	*2*	*3*	*4*	*5*	*6*	*7*
ASSESSMENT							
Informed Consent	x						
Inclusion / Exclusion	x	x					
Medical History	x						
Physical Exam	x						x
Laboratory Tests	x						x
Pregnancy Test	x						
Thyroid Function Test	x						
Urine Drug Screen	x						
ECG	x						x
Vital Signs	x	x	x	x	x	x	x
MINI	x						
HAMD	x	x					x
CGI-I			x	x	x	x	x
CGI-S		x	x	x	x	x	x
HAMA	x	x	x	x	x	x	x
HAD		x			x		x
Covi	x	x			x		x
Raskin	x	x			x		x
Quality of Life Scale		x					x
Adverse Events		x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x
Drug Dispensed/ Returned	x	x	x	x	x	x	x
Final Evaluation		•					x

* Or when the patient discontinued prior to Week 8.

Table VI.B.5-7, Disposition of ITT Safety Population in Each GAD Trial (Studies MD-05, -06, and –07, respectively).

Table VI.B.5 Study MD-05

	Placebo (N=128)	*Escitalopram (N=126)*	*Total (N=254)*
Total Completers	95 (74.2)	97 (77.0)	192 (75.6)
Total Withdrawn for Any Reason	33 (25.8)	29 (23.0)	62 (24.4)
Adverse Event	4 (3.1)	14 (11.1)	18 (7.1)
Withdrawal of Consent	10 (7.8)	7 (5.6)	17 (6.7)
Lost to Follow-Up	8 (6.3)	4 (3.2)	12 (4.7)
Insufficient Therapeutic Response	8 (6.3)	2 (1.6)	10 (3.9)
Protocol Violation	3 (2.3)	1 (0.8)	4 (1.6)
Other	0	1 (0.8)	1 (0.4)

Safety Population
Cross reference: Table 1.2.

Table VI.B.6 Study MD-06

	Placebo (N=142)	*Escitalopram (N=145)*	*Total (N=287)*
Total Completers	114 (80.3)	118 (81.4)	232 (80.8)
Total Withdrawn for Any Reason	28 (19.7)	27 (18.6)	55 (19.2)
Adverse Event	3 (2.1)	8 (5.5)	11 (3.8)
Lost to Follow-Up	10 (7.0)	7 (4.8)	17 (5.9)
Withdrawal of Consent	11 (7.7)	5 (3.4)	16 (5.6)
Insufficient Therapeutic Response	0	4 (2.8)	4 (1.4)
Protocol Violation	2 (1.4)	2 (1.4)	4 (1.4)
Other	2 (1.4)	1 (0.7)	3 (1.0)

Safety Population
Cross reference: Table 1.2.

Table VI.B.7 on next page

Table VI.B.7 Study MD-07

	Placebo (N=157)	*Escitalopram (N=158)*	*Total (N=315)*
Total Completers	123 (78.3)	119 (75.3)	242 (76.8)
Total Withdrawn for Any Reason	34 (21.7)	39 (24.7)	73 (23.2)
Adverse Event	8 (5.1)	14 (8.9)	22 (7.0)
Lost to Follow-Up	12 (7.6)	12 (7.6)	24 (7.6)
Withdrawal of Consent	6 (3.8)	6 (3.8)	12 (3.8)
Insufficient Therapeutic Response	5 (3.2)	2 (1.3)	7 (2.2)
Protocol Violation	3 (1.9)	4 (2.5)	7 (2.2)
Other	0	1 (0.6)	1 (0.3)

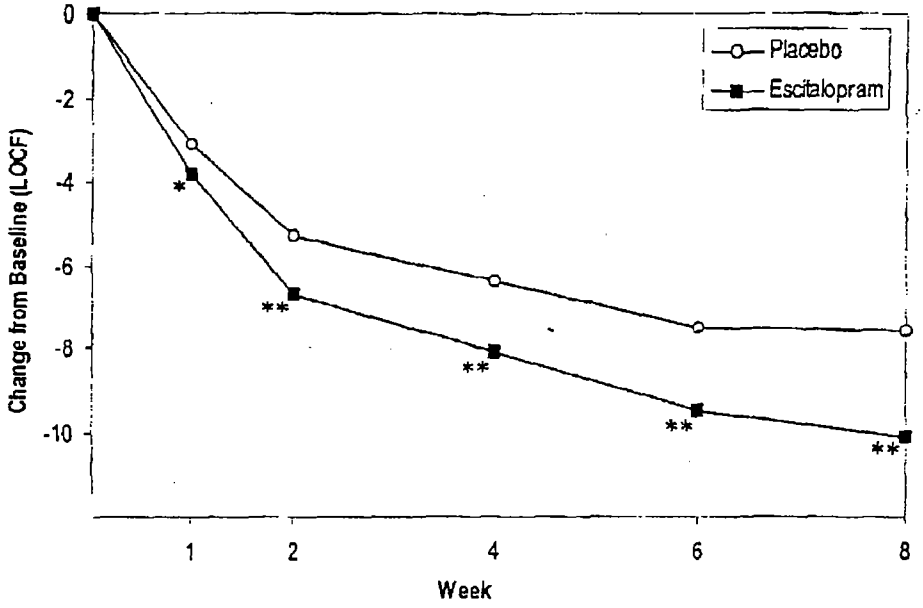
Safety Population
Cross reference: Table 1.2.

Table VI.B.8, Figure VI.B.9 and Table VI.B.10 Efficacy Results of the 3 GAD Trials
Table VI.B.8 HAMA Results

Study	*Mean Change from Baseline to Week 8 – LOCF*	
	Placebo	*Escitalopram*
SCT-MD-05	-7.7	-9.6*
SCT-MD-06	-7.6	-9.2*
SCT-MD-07	-7.4	-11.3**

* Significantly different from placebo, $p < 0.05$.
** Significantly different from placebo, $p < 0.01$.
Cross reference: Tables 3.1A, 3.1C, and 3.1E.

Figure VI.B.9 HAMA Change from Baseline by Visit (LOCF dataset)



***p<0.05, **p<0.01**

Table VI.B.10 Secondary Efficacy Results

Parameter	Mean Change from Baseline to Week 8 – LOCF					
	SCT-MD-05		*SCT-MD-06*		*SCT-MD-07*	
	Placebo	*Escitalopram*	*Placebo*	*Escitalopram*	*Placebo*	*Escitalopram*
HAMA Psychic Anxiety	-4.0	-5.3**	-3.9	-5.5**	-3.8	-6.4**
CGI-S	-0.9	-1.2*	-0.9	-1.2**	-0.8	-1.4**
CGI-I	2.8	2.6	2.8	2.6 *	2.8	2.4**

* Significantly different from placebo, $p < 0.05$.
** Significantly different from placebo, $p < 0.01$.
CGI-I value at Week 8 only.
Cross reference: Tables 3.2A-3.4A, 3.2C-3.4C, and 3.2E-3.4E.

Table VII.E.1.

Serious Adverse Events — GAD Extension Study (SCT-MD-17)

Patient Number	*Age (years)/ Gender*	*Adverse Event Preferred Term*	*Day of SAE Start*	*Relationship to Study Medication*
5078	46 / M	Suicide Attempt**	126	Not Related
5128	37 / F	Breast Cancer*	75	Not Related
5252	45 / M	Inflicted Injury	47	Not Related
6019	44 / F	Diabetes Mellitus	177	Possibly Related
6116	33 / M	Inflicted Injury	85	Not Related
6297	37 / F	Skin Carcinoma	105	Not Related
7108	62 / M	Hepatic Enzymes Increased	11	Possibly Related
7187	31 / F	Suicide Attempt*	30	Not Related
		Non-accidental Overdose*	30	Not Related
7224	60 / F	Ovarian Tumor Benign*	61	Not Related
7230	21 / F	Upper Respiratory Tract Infection	132	Not Related
7258	56 / F	Basal Cell Carcinoma	18	Not Related

* Discontinued due to SAE.
**Died (See Section 9.1).
All patients in Study SCT-MD-17 received open-label escitalopram treatment.
Day of SAE start = SAE start date – start date of study medication +1.
M = Male; F = Female.
Cross reference: Table 4.2.

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Table VII.E.2. Selected SAEs (refer to Section VII E of the Review)

Selected SAEs in GAD Trials

- **Increased hepatic enzymes** in **S 7108** (in the GAD ongoing extension study MD-17) which appeared to be due to a viral (CMV) hepatitis. The S was a 62 year old male who had elevated alkaline phosphatase, ALT and AST (159, 2582 and 1676 U/l, respectively) at his last study visit 3 days after completing 7 days of SCT between December 8 and December 14. All other chemistry and hematology measures were within normal limits at this last study visit and a CT scan showed a normal liver.

  Treatment was discontinued due to "flu-like" symptoms from December 12th to the 15th of 2001. However, the S also had flu-like symptoms several weeks before SCT treatment was initiated. Yet, his baseline laboratory parameters (including LFTs) were within-normal-limits (obtained on December 7th).

  After treatment was terminated, CMV IgG antibodies were revealed on January 3rd of 2002 and became non-detectable on March 8th. Liver function tests (LFTs) returned to normal by 2/4/02. It appears that this SAE was due to a viral hepatitis, noting the patient experience flu-like symptoms before SCT exposure, as well as during treatment, as above. However, a potential role of study drug with elevated LFTs cannot be ruled out (such as SCT treatment exacerbated effects of a pre-existing viral hepatitis on LFTs).

  - **Diabetes mellitus** was diagnosed in **S6019** after 176 days of SCT treatment who was a 45 year old woman with a positive family history of diabetes. This S showed elevated glucose levels at the completion of a lead-in study (after 58 days of SCT in Study MD-06) and again upon completion of the extension study (Study 17 after 176 days of treatment). Glucose levels on these time-points were 204 and 260 mg/dl, respectively and urinalysis was positive for ketones and glucose. At screening for Study MD-06 her glucose levels were within normal limits (98 mg/ml). She was treated with glipizide and her glucose levels normalized. Given here positive family history and her age, this SAE is most likely due to either an underlying/undiagnosed condition or due to risk factors. However, a potential influence of SCT treatment on this event cannot be ruled out.

Selected SAEs in Other trials:

- **Pulmonary embolism in S8041**. The 1/7/03 response from the sponsor clarified that the study drug assigned to #8041 remains blinded at this time (Study SCT-MD-20 remains blinded). This 36 year old was reported to have no concomitant medications or illnesses. She received blinded study drug for approximately 2 months prior to being seen in an emergency room due to experience pain when she breathed. While there is no mention of diagnostic tests (the sponsor provided a copy of the MedWatch report on this S), but the S was treated on heparin followed by coumadin for a 6 month period. The "physicians were unaware why this event occurred..." There is no comments in the Med Watch report about potential risk factors (e.g. whether or not the patient was a smoker, use of oral contraceptive agents, or other possible factors). It is not clear what caused this event and given the paucity of information and reports of risk factors a relationship to the study drug cannot be ruled out. Nevertheless, the study drug remains blinded (could be placebo) and SSRIs are not known to be associated with this type of event.

- **Convulsions** in **S1532** (in blinded study 99269) who was 28 year old female with a history of a seizure at 6 years old. Labeling already includes a precautionary statement regarding patients with a history of seizures. According to updated information on this S (in a 3/12/03 amendment submission) blinded study drug in this S was found to be SCT.
  - The **inflicted injuries** listed in Panel 16 of the ISS included a dog bite (S1201), automobile accident (S7292, S8512), slipped on ice (S2012), fracture of lateral maleolus (S2340), stuck by a car (S6010) and a 74 year old who had an accident in her home and was continued on SCT (S5698), and S5495 was an 81 year old man who fell and had fracture of the femur, but continued the study after being discharged from the hospital (as described in a 1/7/03 response to a request

for additional information). S5495 in Study 99258 fell and fractured his femur, but continued study drug after being treated for the fracture and his hospital discharge. The cause of the fall is unknown (according to a 1/7/03 response to a request for more information on this S). However, this S was receiving multiple cardiac related drugs.

- **Syncope and inflicted injury** in **S 6010** (on blinded study drug) who was a 28 year old SCT treated woman with a history of multiple fainting episodes (between ages 12-16 years). She had worked long hours on April 2nd and was not eating well, when she became nauseated, jittery, tired and had a blood pressure of 98/60. The next day she had nausea, felt diaphoretic and momentarily blacked out while driving (hit trees, uninjured). She recovered the same day and was withdrawn from the study. She was started on sertraline for her major depressive disorder.
- **Pulmonary edema and myocardial infarction in S5361** in Study 99067 who was an SCT treated S and had several risk factors (86 year old, hypertension) and a past history of myocardial infarction.
- **Cerebrovascular disorder in S5612** who died and is described under Section VII D on deaths.
- **Transient ischemic attack in S5646** who was a 79 year old with a history of hypertension (both are risk factors for the event). This S experienced an episode malaise and aphasia on 1/11/02 lasting for a few hours and was hospitalized, recovered and was discharged. SCT treatment began in the previous year (1/1/01) and the S was continued in the study after this SAE.
- **Fever and macular rash in S6408** in study 99270 who discontinued study drug due to these SAEs. Study in drug in this S was listed in a 3/12/03 amendment submission as being SCT (study drug was previously blinded and listed as such, in the original submission).

- **S1184** (panel 16 on page 34/36 of ISS) **had hypomania** on blinded drug (study 99269). The study drug in this 38 year old male S was unblinded and found to be SCT (as listed in Panel 1 in s 3/12/03 amendment submission with updated submission). Study drug was discontinued in this S due to hypomania. This event could be drug-related or due to undiagnosed bipolar disorder. Hypomania is not a new or unexpected event.

Table VII.E3-4 Serious Adverse Events in Other Trials
Table VII.E3

Serious Adverse Events — Other Escitalopram Studies (Cutoff Date: July 1, 2002)

Study Number	*Patient Number*	*Age (years)/ Gender*	*Adverse Event (Preferred Term)*	*Day of SAE Start*	*Relationship to Study Medication*
SCT-MD-11	8314	41/F	Uterine fibroid	205	Not Related
	8336	50/F	Uterovaginal Prolapse	245	Not Related
SCT-MD-20	8041*	36/F	Embolism Pulmonary	55	Not Related
SCT-MD-21	21101*	22/F	Anxiety	45	Related
			Depression	45	Related
			Suicidal tendency	45	Related
SCT-MD-26	6010*	45/F	Inflicted injury	3	Not Related
PLACEBO					
99269	1275*	40/F	Depression	82	Possible
ESCITALOPRAM					
99067	3151	42/F	Arthropathy	99	Not Related
99258	5275	81/F	Uterine neoplasm	339	Not Related
	5361	86/F	Pulmonary oedema	360	Not Related
			Myocardial infarction	360	Not Related
	5495	81/M	Inflicted injury	265	Not Related
	5497	80/M	Surgical intervention	249	Not Related
	5590*	67/M	Hepatic neoplasm malignant	342	Not Related
	5612**	76/F	Cerebrovascular disorder	262	Not Related
	5646	79/F	Transient Ischemic attack	353	Not Related
	5698	74/F	Inflicted injury	315	Not Related
	5788	82/M	Anaemia	183	Not Related
			Breath shortness	183	Not Related
	5794	80/F	Depression aggravated	237	Not Related
SCT-MD-11	8055*	57/M	Coma	336	Possibly Related
			Suicide Attempt	336	Possibly Related
	8512*	34/M	Inflicted injury	4	Not Related
	8517	22/F	Surgical Intervention	320	Not Related

Continued on next page.

Table VII.E3, continued.

Serious Adverse Events — Other Escitalopram Studies (Cutoff Date: July 1, 2002)

Study Number	*Patient Number*	*Age (years)/ Gender*	*Adverse Event (Preferred Term)*	*Day of SAE Start*	*Relationship to Study Medication*
SCT-MD-19	6010*	28/F	Inflicted Injury	2	Not Related
			Syncope	1	Not Related
VENLAFAXINE					
99067	3261**	65/M	Myocardial Infarction	96	Not Related

* Discontinued due to SAE.
**Died.
Day of SAE start = SAE start date – start date of study medication +1.
M = Male; F = Female; N/A not available.
Cross reference: Table 4.2.

Table VII.E4

Serious Adverse Events in Other Trials

Of Subjects in Which Study Drug was Unblinded (subsequent to the original NDA submission) as Provided in a 1/7/03 Amendment Submission

Study Number	*Patient Number*	*Age (years)/ Gender*	*Adverse Event (Preferred Term)*	*Day of SAE Start*	*Relationship to Study Medication*
ESCITALOPRAM					
99269	1184*	38/M	Hypomania	151	Probable
	1532*	27/F	Convulsions	17	Not Related
99270	6802	45/M	Inflicted injury	140	Not Related
	6408*	35/F	Fever	200	Probable
			Macular rash	200	Not Related
	6730*	29/F	Suicide Attempt	101	Possible
99505	2012	48/F	Inflicted injury	177	Not Related
	2113**	76/F	Sudden death	149	Not Related
	2116	39/F	Nonaccidental overdose	100	Not Related
			Pneumonia	212	Not Related
	2145	62/F	Inflicted injury	156	Possible
			Inflicted injury	170	Not Related
	2228	55/F	Bronchitis	117	Not Related
	2304	57/F	Surgical intervention	70	Not Related
			Menstrual disorder	134	Not Related
SCT-MD-26	6010*	45/F	Inflicted injury	3	Not Related
PLACEBO					
99269	1201*	43/M	Inflicted Injury	157	Not Related
	1275*	40/F	Depression	81	Possible
99270	6749*	26/F	Depression	28	Possible
	6794	42/F	Asthenia	160	Not Related
PAROXETINE					
99270	7292	27/F	Inflicted injury	63	Not Related
99505	2084*	66/M	Bronchitis	158	Not related
	2229*	58/F	Nonaccidental overdose	262	Not Related
	2230	50/F	Pain	158	Not Related
	2275	59/F	Chest pain	201	Not Related
	2340	35/F	Inflicted injury	112	Not Related
	2400*	47/F	Pharyngitis	90	Not Related

* Discontinued due to SAE.
**Died.
@ Discontinued from the study due to flu-like symptoms.
Day of SAE start = SAE start date – start date of study medication +1.
M = Male; F = Female.

Tables VII.F. 1-3, Adverse Dropout Listings for Completed Trials, MD-05, MD-06 and MD-07, respectively.

Table VII.F.1 Study MD-05 (continued on the next page)

Treatment Group/ Patient Number	*Age (yrs)*	*Sex*	*AE Start Day*	*AE (Preferred Term)*
PLACEBO				
5007	31	M	8	Appetite increased
			8	Depression
			8	Fatigue
			8	Somnolence
5021	27	M	30	Anxiety attack
5068	44	F	9	Arthralgia
			9	Rash
5100	30	M	3	Anxiety
ESCITALOPRAM				
5029	49	M	29	Dizziness
			29	Somnolence
5065	52	F	18	Nausea
			18	Metallic taste
5105	39	F	12	Edema of extremities
5107	43	M	2	Insomnia
			2	Irritability
			1	Jitteriness
5112	32	M	6	Headache
5131	23	F	1	Headache
			1	Nausea
5138	25	F	3	Abdominal pain
			3	Diarrhea
5145	46	F	6	Headache
			4	Sinusitis

Table VII.F.1 Study MD-05, Adverse Dropouts, continued

Treatment Group/ Patient Number	*Age (yrs)*	*Sex*	*AE Start Day**	*AE (Preferred Term)*
5154	51	F	43	Diarrhea
			42	Nausea
			43	Vomiting
5211	65	M	6	Gastroesophageal reflux
5236	41	F	3	Emotional lability
			3	Fatigue
5249	57	F	1	Nausea
5270	62	M	34	Hives
5318	28	F	2	Anxiety
			9	Headache
			2	Insomnia
			2	Dry mouth
			9	Palpitation
			9	Tachycardia

*AE Start Day = AE Start Date – Date of First Dose +1.
Safety Population
Cross reference: Table 7.3.

Table VII.F.2 Study MD-06, Adverse Dropouts

Treatment Group/ Patient Number	*Age (yrs)*	*Sex*	*AE Start Day**	*AE (Preferred Term)*
PLACEBO				
6051	42	M	2	Nausea
6182	54	M	16	Depression aggravated
6239	56	M	9	Headache
ESCITALOPRAM				
6043	44	F	1	Nausea
			1	Vomiting
6047	24	M	2	Panic Reaction
6055	44	F	9	Fatigue
6079	31	F	27	Insomnia
			27	Nervousness
6083	24	M	9	Depersonalization
			9	Lethargy
6093	34	F	4	Insomnia
			4	Nausea
			4	Sweating increased
6211	33	M	2	Sluggishness
6231	30	F	3	Influenza-like symptoms

* AE Start Day = AE start date - Date of First Dose + 1.
Safety Population
Cross reference: Table 7.3.

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Table VII.F.3 Study MD-07: Adverse Dropouts in Placebo Subjects

Treatment Group/ Patient Number	*Age (yrs)*	*Sex*	*AE Start Day*[a]	*AE (Preferred Term)*
PLACEBO				
7073	46	F	31	Panic Reaction
7088	77	F	2	Breath Shortness
			2	Dizziness
			2	Headache
			2	Somnolence
7133	51	F	9	Anxiety
7150	45	F	25	Headache
7156	28	M	9	Abdominal Discomfort
			3	Apathy
			4	Breath Shortness
			6	Constipation
			9	Nervousness
7214	25	M	31	Anxiety
7227	33	F	23	Depression
7375	23	M	1	Headache

Continued on the next page.

Table VII.F.3, continued. Study MD-07: Adverse Dropouts in Escitalopram Subjects

Treatment Group/ Patient Number	*Age (yrs)*	*Sex*	*AE Start Day*[a]	*AE (Preferred Term)*
ESCITALOPRAM				
7013	58	F	12	Disorientation
			12	Dizziness
			12	Headache
			12	Hypertension*
7069	51	F	2	Fatigue
7086	51	F	2	Fatigue
			2	Somnolence
7107	31	F	3	Chills
			3	Diarrhea
			3	Headache
			3	Insomnia
			3	Nausea
7131	63	M	2	Myalgia
7149	36	F	8	Panic Reaction
			2	Tremulousness/Nervousness
7159	49	F	3	Lethargy
7179	44	F	1	Dizziness
			-4[b]	Fatigue
			1	Nausea
			1	Paraesthesia
			1	Vomiting
7186	39	M	11	Somnolence
7223	31	F	1	Anorgasmia
7233	67	F	2	Panic Reaction
7276	41	F	2	Libido Decreased
7284	42	M	2	Nausea
			1	Somnolence
7299	53	F	1	Anxiety
			1	Insomnia

[a] AE Start Day = AE Start Date – Date of First Dose +1.
[b] Started during the placebo lead-in period.
* Serious adverse event.
Safety Population
Cross reference: Table 7.3.

Table VII.F.4 Selected Adverse Dropouts (refer to Section VII.F of the review).

S7110 (a 30 year old female on no concomitant medications and no medical conditions other than GAD) had first degree AV block (PR interval of 212 msec compared to 208 msec at baseline). This event resulted in cessation of treatment after 14 days of SCT during Study MD-17 (she received 56 days of SCT in the lead-in study, MD-07). However, based on the following it appears that the first degree AV block was a pre-existing condition. The ECG changes (observed on 12/19/01while on the study drug) relative to a baseline ECG (obtained at baseline for the lead-in study) were considered by the investigator as "not clinically significant." Also subsequent ECGs continued to show a similar first degree AV block, including an ECG obtained by a cardiologist 19 days after treatment cessation.

Upon request the sponsor provided the following information in a 3/12/03 amendment submission:

> PR interval was up to 20 msec upon repeat ECGs (ranging from 212 to 220 msec) during SCT treatment and decreased after cessation of study drug to 207 and 164 msec at one day post-treatment and one week post-treatment cessation, respectively. HR at baseline was 62 bpm, but remained within the range 60-69 bpm and remained similar after treatment cessation. QT and QTc intervals (Bazett's and Frediricia, each) ranged from 383 to 423. Given these observations before, during and after treatment, first degree AV block could be drug-related. However, the S did not appear to have AEs associated with or showing a clear temporal relationship with the observed PR prolongation. Finally, first degree AV block is not uncommon in the general population (such as well trained athletes or young adults) or can be reflecting high vagal tone. Also given that later (19 days after treatment cessation) this AV block was again observed, no data provided).

Table VII.H. 1

Most Frequent (Incidence > 5% in the Escitalopram Treated Group)
Treatment Emergent Adverse Events

In the 3 GAD Trials

Preferred Term	*Placebo (N=427) n (%)*	*Escitalopram (N=429) n (%)*
Patients with at least one TEAE	302 (70.7)	358 (83.4)
Headache	71 (16.6)	101 (23.5)
Nausea	32 (7.5)	78 (18.2)
Ejaculation Disorder[a]	3 (1.5)	26 (14.3)
Somnolence	28 (6.6)	56 (13.1)
Insomnia	24 (5.6)	51 (11.9)
Dry Mouth	23 (5.4)	38 (8.9)
Diarrhea	25 (5.9)	36 (8.4)
Upper Respiratory Tract Infection	33 (7.7)	33 (7.7)
Fatigue	9 (2.1)	33 (7.7)
Libido Decreased	9 (2.1)	29 (6.8)
Anorgasmia[b]	1 (0.4)	14 (5.7)
Constipation	15 (3.5)	22 (5.1)

Based on Studies SCT-MD-05, SCT-MD-06, and SCT-MD-07.
[a]Percentage is relative to the number of male patients (placebo, N=195; escitalopram, N=182).
[b]Percentage is relative to the number of female patients (placebo, N=232; escitalopram, N=247).
Cross reference: Table 4.6.

Table VII.I.1

Criteria for Potentially Clinically Significant Laboratory Values

Laboratory Parameter	*SI Units*	*US units*	*Conversion Factor**	*PCS Criteria*	
				Low Values	*High Values*
HEMATOLOGY					
Hemoglobin	mmol/l	g/dL	1.611	≤ 0.9 * LNL	—
Hematocrit	1	%	100	≤ 0.9 * LNL	—
Eosinophils	%	%	1	—	≥ 10
Neutrophils segs	%	%	1	≤ 15	—
Platelet Count	GI/L	$10^3/\mu L$	1	≤ 75	≥ 700
WBC	GI/L	$10^3/\mu L$	1	≤ 2.8	≥ 16
CHEMISTRY					
Alkaline Phosphatase	U/L	U/L	1	—	≥ 3 * UNL
ALT (SGPT)	U/L	U/L	1	—	≥ 3 * UNL
AST (SGOT)	U/L	U/L	1	—	≥ 3 * UNL
LDH	U/L	U/L	1	—	≥ 3 * UNL
Blood Urea Nitrogen	mmol/l	mg/dL	2.801	—	≥ 10.7
Calcium	mmol/l	mg/dL	4.008	≤ 1.75	≥ 3.0
Cholesterol	mmol/l	mg/dL	38.67	—	≥ 7.8
Creatinine	μmol/l	mg/dL	0.011	—	≥ 175
Potassium	mmol/l	mEq/L	1	≤ 3	≥ 5.5
Sodium	mmol/l	mEq/L	1	≤ 125	≥ 155
Total Bilirubin	μmol/l	mg/dL	0.058	—	≥ 34.2
URINALYSIS					
Protein				—	≥ ++
Glucose				—	≥ ++

*Conversion factor from SI to US units
LNL = Lower Normal Limit of Laboratory Reference Range
UNL = Upper Normal Limit of Laboratory Reference Range
GI/L = $10^9/L$

Table VII.J. 1

Mean Values for Vital Signs and Body Weight

For the 3 GAD Trials

Parameter		*Placebo (N = 420)*	*Escitalopram (N = 421)*
Systolic BP (mm Hg)	Baseline	119.7	119.9
	Change	-0.4	-0.5
Diastolic BP (mm Hg)	Baseline	76.1	75.9
	Change	0.8	0.6
Pulse Rate (bpm)	Baseline	72.9	73.5
	Change	-0.7	-1.6
Weight (lb)	Baseline	171.6	170.9
	Change	0.01	0.11

Based on Studies SCT-MD-05, SCT-MD-06, and SCT-MD-07.
N = Number of treated patients with both baseline and at least one post-baseline assessment.
BP = Blood pressure.
Change = Mean change from baseline at endpoint.
Cross reference: Tables 5.3 through 5.6.

Table VII.J. 2

Incidence of Potentially Clinically Significant Changes in Vital Signs and Body Weight

For the 3 GAD Trials

Parameter	*PCS Criteria*	*Placebo (N = 420) n (%)*	*Escitalopram (N = 421) n (%)*
Systolic Blood Pressure (mm Hg)	≥ 180 and increase ≥ 20	2 (0.5)	1 (0.2)
	≤ 90 and decrease ≥ 20	4 (1.0)	2 (0.5)
Diastolic Blood Pressure (mm Hg)	≥ 105 and increase ≥ 15	3 (0.7)	1 (0.2)
	≤ 50 and decrease ≥ 15	2 (0.5)	3 (0.7)
Pulse (bpm)	≥ 120 and increase ≥ 15	2 (0.5)	0
	≤ 50 and decrease ≥ 15	1 (0.2)	2 (0.5)
Body Weight (lb)	Increase ≥ 7%	0	5 (1.2)
	Decrease ≥ 7%	6 (1.4)	6 (1.4)

Based on Studies SCT-MD-05, SCT-MD-06, and SCT-MD-07.
N = Number of treated patients with both baseline and at least one post-baseline assessment.
Cross reference: Table 5.1.

Attachment 1.

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Table 2 from Dr. David Gan's 8/12/02 Review of NDA 21-323 for the MDD Trials as Described in Section VII.K.1. of the Present Review (the bolded results are the mean change from baseline to treatment endpoint/week 8 of treatment of each ECG parameter excluding invalid ECGs).

	Placebo		*Escitalopram*		*Citalopram*	
ECG Parameter	*(N=592)*		*(N=715)*		*(N=408)*	
	540	0.3	650	-2.3	367	-2.4
Heart Rate	**527**	**0.3**	**625**	**-2.2**	**351**	**-2.7**
	540	0.0	650	0.6	367	0.0
QRS Interval	**527**	**0.0**	**625**	**0.5**	**351**	**0.1**
	540	0.6	648	0.3	366	-0.6
PR Interval	**527**	**0.3**	**623**	**0.6**	**350**	**-0.5**
	540	-0.2	650	7.5	367	7.6
QT Interval	**527**	**-0.0**	**625**	**7.4**	**351**	**8.2**
	540	0.8	650	2.0	367	1.6
QTcB Interval (Bazett)	**527**	**0.9**	**625**	**1.9**	**351**	**1.2**
Adjusted QTcB Interval	540	1.1	650	1.8	367	1.7
(Bazett)	**527**	**1.5**	**625**	**1.9**	**351**	**1.5**
QTcF Interval	540	0.4	650	4.0	367	3.7
(Fridericia)	**527**	**0.5**	**625**	**3.9**	**351**	**3.7**
Adjusted QTcF Interval	540	0.6	650	4.0	367	3.7
(Fridericia)	**527**	**0.9**	**625**	**4.1**	**351**	**3.7**

Revisions are indicated in bold.

Adjusted QTc intervals are the least squares means obtained from the ANCOVA model with treatment and study as factors and baseline value as covariate.

Attachment 2.

Appears This Way
On Original

Conclusions and Recommendations Section of a Clinical Review of the 11/12/02 Response Submission under NDA 21-322 (refer to Section IX).

The following are reviewer comments regarding the results provided in this submission. Study SCT-MD-01 was not designed for the purpose of examining QT interval against plasma levels of SCT. Therefore, inconsistent or negative results for a potential correlation between QT interval and SCT plasma levels revealed in this study are difficult to interpret. These results do not provide adequate evidence for ruling out a potential QT effect of SCT treatment or for ruling out a potential relationship between QT interval and SCT plasma levels or dose levels (noting that plasma levels may not be adequate specific and/or reliable). It is also noted that the justification for using a 25 ng/ml cut-off for SCT plasma levels in Table 1 in the submission was not provided and the rationale is not clear. Refer to previous Clinical reviews under NDA 21-323 and NDA 21-440 for a discussion on the issue of QT and other related safety findings and SCT treatment.

The Office of Drug Safety (ODS) conducted a postmarketing safety review (dated 9/30/02) of adverse event reports (AERS) cases of QT prolongation and other potentially related events with citalopram treatment (the racemate). Other selective serotonin reuptake inhibitors and other antidepressant medications were included in this data analysis in which reports of the following events were enumerated: QT or QTc prolongation, torsades de pointes, cardiac arrest, death (sudden/unexplained). This postmarketing data analysis revealed a numerical trend for the greatest percentage (1.99%) of QT prolongation and related events (as previously listed) in citalopram treated patients compared to patients on the other drugs. The case series reviewed by the ODS consultant showed "that citalopram may be associated with dose-related QT prolongation that may be of clinical significant at therapeutic doses in patients with other risks factors for arrhythmia." A review of the literature on this topic was also conducted. ODS recommended the following for citalopram labeling (refer to the 9/30/02 ODS consultative review for further details):

"It would be prudent to advise caution in prescribing citalopram to patients with risk factors for developing QT prolongation and ventricular arrhythmia [ ]

[ ]

Clinical reviews of NDAs 21-323 and 21-440 provided similar comments or recommendations regarding patients with potential risk factors for QT prolongation, bradycardia and other related events. The 9/30/02 ODS consultation was requested by the Division Safety Group. A Division Safety Group review/memo to the file cannot be found in DFS regarding the ODS consultative request or as a follow-up to the ODS review that describes the above observations and recommendations.

A Safety Group consult is recommended to review the present response submission on QT information (as requested in the 8/14/02 Approval Letter) and to provide recommendations for labeling for SCT and citalopram, particularly in light of more recent observations and recommendations made by the ODS consultant. Consideration may also be given to a further examination of potential effects of SCT and citalopram on ECG related events (QT prolongation, bradycardia and related arrhythmias). A study specifically designed to examine this effect that employs a wide fixed dose range with a parallel group design may be considered. Consideration to a further examination of existing QT and other related ECG data from other citalopram and/or

SCT trials already conducted by the sponsor may also be considered (perhaps Phase I trials, also refer to previous Clinical reviews under NDAs21-323 and 21-440 for some suggestions to consider). A discussion of QT and other ECG and safety related observations (including bradycardia and other potentially related events) regarding special populations is also described in Clinical reviews of NDAs 21-323 and 21-440. It is important to note that these Clinical reviews were conducted and filed prior to receipt of new QT related information submitted under these NDAs. These later QT related submissions were under review by the Safety Group, as previously described, during the review cycles of these NDAs. One final note to be considered by the Safety Group regarding the ECG data in the present 11/12/02 submission is that the sponsor does not explicitly indicate that the ECG data excludes any and all data obtained from invalid ECG readings, as revealed by DSI.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Brugge
7/1/03 10:19:04 AM
MEDICAL OFFICER

Paul Andreason
8/27/03 01:55:33 PM
MEDICAL OFFICER
I recommend that the Division take an Approvable Action on this supplement. See my memo to file dated 8/27/03.

REVIEW AND EVALUATION OF CLINICAL DATA

Response to Approvable Letter dated 9/26/03

NDA:	21-323 SE1-003 (oral tablet formulation) 21-365 SE1-004 (oral solution formulation)
Sponsor:	Forest Laboratories, Inc.
Drug	
Established Name:	Escitalopram oxalate
Chemical Name:	(+)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
Code Name:	Lu 26-054
Formulation:	10 mg and 20 mg encapsulated tablets (also 20 and 40 mg citalopram encapsulated tablets and placebo were employed)
Indication:	Generalized Anxiety Disorder (GAD)
Dates of Submission:	October 20, 2003, EDR date 10/27/03, received on 10/31/03
Materials Reviewed:	Response to 9/26/03 Approvable Letter
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	11/4/03

II. Background

This submission is in response to the 9/26/03 Approvable Letter. This review is to assist the Team Leader and the Division Director in the regulatory processing of this supplemental NDA.

III. Response to the Approvable Letter

A. Labeling. Based on the labeling provided by the sponsor (Attachment 1 of the submission), the sponsor has accepted our labeling changes and has responded to our proposal to update specified sections, as indicated in our 9/26/03 Approvable Letter (based on a review of highlighted text sections and changes indicated by strikeouts in proposed labeling in Attachment 1).

Refer to Section IV for recommendations regarding proposed labeling.

B. Safety Update.

Serious Adverse Events. See Table 1 in Attachment 2 of the submission for a listing of serious adverse events reported between July 2, 2002 and September 1, 2003. Overall serious adverse events (SAE's) failed to reveal new or unexpected events that are not already described in labeling or were events that were likely to be associated with other factors (e.g. pre-existing conditions, pre-existing risk factors, or other factors) or were events that failed to show a temporal relationship with treatment that would be consistent with the drug-related event (the sponsor provided brief narratives for each SAE).

However, the following SAE's may be exceptions and are described for reasons provided below.

1. Two SAE's of gastrointestinal events requiring surgical intervention in which the role of the study drug must be considered in the absence of additional information, as described below. Current approved labeling describes gastrointestinal-related AE's in various subsections of the Adverse Reactions section of labeling.

Colon Obstruction requiring surgery in a 49-year-old male (subject 0029033 in Study M.D.-12) who is not on any concomitant medication and did not have any medical conditions described in the narrative. This subject required surgical removal of 15 inches of his colon due to a "twisted bowel" after approximately one month of treatment with 10-20 milligrams a day of escitalopram.

Gastric ulcer resulting in a gastrectomy in a 63-year-old male (subject 166-1 in study 99862) with no history of medical conditions described in the narrative. This event occurred after 12 days of treatment with 10 mg of escitalopram, daily. The patient was treated with lansoprazole and a sodium alginate/sodium bicarbonate/calcium carbonate. In the absence of other information one cannot rule out a role of the study drug in this event.

As described in Dr. Paul Andreason's memo to the file dated 8/27/03, class labeling for SSRI associated abnormal bleeding events (include gastrointestinal bleeding) is under consideration by the Division. Current approved labeling also includes gastrointestinal events in various section of labeling. However, the sponsor should obtain more information on the above subjects in an effort to ascertain the etiology of the events and these events should be considered with other gastrointestinal events being considered for drug-class labeling by the Division.

2. Syncope, sleep disorder, twitching that may be suggestive of seizures, in a subject described below. In the absence of additional information one must suspect a potential role of the study drug, although the subject was able to continue in the study as noted below (after a series of 3 episodes, suggestive of seizures). The Office of Drug Safety is currently examining postmarketing data for a signal of seizures with Celexa.®

This 37-year-old male (subject S1005 in study 99769) had three "fainting" episodes over a two day period following "very strenuous work at high outdoor temperatures." The first episode was followed by prolonged sleep of up to five hours and the other two episodes were also associated with "muscular trembling, localize mainly to the fingers." Each episode lasted 5-10 minutes and was not associated with loss of feces or urine. The narrative does not indicate a diagnosis or a differential diagnosis, results of diagnostic tests or other clinical assessments and does not specify when this subject received treatment (a dose of "10, 20 mg" of escitalopram).

3. Two SAEs in which Pulmonary Embolism was Diagnosed and Treated
Given the paucity of information provided on both of subjects described below, one must consider a potential role of the study drug. Pulmonary embolism is not known to be

associated with escitalopram, escitalopram and other SSRIs and can occur in women with risk factors such as when taking hormonal replacement treatment, smoking, age, varicose veins among other factors. The sponsor should be advised to obtain further information on these subjects, such as the presence of known to risk factors, results of diagnostic tests and other relevant information to help determine the etiology of these SAE's.

Angina in a 55-year-old female (subject 129 in Study 99812) who had received escitalopram 10 mg daily for seven days when she was hospitalized for chest pain. A **CT scan revealed bilateral pulmonary embolism** and the patient was treated with anticoagulants. This subject was not receiving concomitant medications and the narrative does not describe any pre-existing medical conditions or risk factors that may have contributed to this SAE. Therefore, given the limited information, a potential role of the study drug must be considered.

The Clinical Review of the original S-003 submission describes one SAE of pulmonary embolism in a 36-year-old female (subject 8041) while taking blinded study drug who was treated with anticoagulants. The narrative on this subject did not describe any underlying illness or risk factors that may have contributed to this SAE.

4. Myocardial infarction occurred in a 58 -year-old male (subject 2780 in study 99815) receiving no concomitant medications and who had no medical conditions described in the narrative. This subject was hospitalized for sudden chest pain and the diagnosis of myocardial infarction was "confirmed" by EKG (the narrative does not mention any laboratory assessments). Given the limited information in the narrative and that this subject was not described as having pre-existing cardiovascular disease, one must consider a potential role of the study drug in this SAE. However, the patient had several risk factors (age and gender) and had received 94 days of blinded study drug before this event occurred, suggesting that this event could be due to underlying or pre-existing factors, rather than the SAE being drug-related. Further information on this subject should become available, once the study drug is unblinded and more information is received on this subject.

Worldwide Literature Update

A literature search was conducted by the sponsor for publications on escitalopram and citalopram treatment in patient populations with GAD, Major Depressive Disorder and other disorders (published between the dates of September 1, 2002 and September 30, 2003).

This literature search is described as identifying no new reports for either of the two drugs in GAD patients.

The results of the literature search for other non-GAD patient populations are described (Tables 1 and 2 in Attachment 4 of the submission). Table 3 of Attachment 4 in the submission describes case reports. Six out of 17 case reports were of primarily elderly patients who developed hyponatremia or SIADH associated with citalopram treatment. Several of these patients were taking other concomitant medications and/or had active

medical conditions. Although, a few exceptions to this observation existed (a few elderly patients were generally healthy and taking no concomitant medications).

Two out of 17 case reports were of two patients with serotonin syndrome who were receiving both escitalopram and linezolid (one of these patients had additional concomitant medications).

C. Foreign Regulatory Status Update

The sponsor provides the foreign regulatory status update of Lexapro® for treatment of GAD as of October 2, 2003. An application was approved in Mexico for GAD and applications are pending in [ ] which have a current status of pending.

IV. Conclusions and Recommendations

The safety update information in this response submission to the 9/26/03 Approvable Letter provides results that do not change overall conclusions regarding the safety of escitalopram, as described in the Clinical Review of S-013 and in previous reviews under this NDA and under NDA 21-440. From a clinical perspective, escitalopram (at the recommended dose) is considered to be adequately safe in the study population examined in clinical trials supporting the efficacy claim for GAD. Note CMC issues regarding the S-003 submission (also refer to Approvable Action Letter with CMC Issues) that may in turn, impact on at least efficacy conclusions.

Most of labeling changes indicated in the 9/26/03 Action Letter were accepted by the sponsor and sections were updated upon our request.

The following are recommendations relevant to specific sections of the current submission and proposed labeling.

1. It is recommended that the sponsor provide additional information on the following subjects (e.g. results of diagnostic and other clinical assessments, presence of underlying illness and risk factors, and complete medication and study drug information, that would help to determine the etiology of the events:

a. Two subjects diagnosed with pulmonary embolism (subject 129 in protocol 99812 and subject 8041 who was described in the original submission on SAEs in "Other Trials").

b. Two subjects with life-threatening gastrointestinal events requiring surgical interventions (subject 002903 in Study MD-12 and subject 166-1 in study 99862).

2. It is recommended that the Office of Drug Safety (which is currently reviewing postmarketing data for a potential signal of seizures associated with citalopram) is made aware of events of seizures reported with escitalopram, including subject S1005 in study 99769. Furthermore, additional information on this subject should be obtained that may shed light on the etiology of the event (results of diagnostic tests and other relevant clinical assessments, among other clinical information that may be useful in determining the etiology). Given the information available at this time, the sponsor's update in the section on "Seizures" (page 7 of their proposed labeling) is reasonable.

5. An OCPB consult is recommended regarding the case reports of a potential citalopram-linezolid interaction resulting in development of serotonin syndrome with regards to escitalopram, citalopram labeling and potentially for Zyvox® labeling. It is noted that approved labeling for Zyvox® indicates the following under Drug-Drug Interactions:

> *"Serotonergic Agents:* The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20-mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan. The effects of other serotonin re-uptake inhibitors have not been studied. "

6. The following are recommendations regarding sections of labeling that were modified by the sponsor in response to our request indicated in the Approvable Letter:

- On page seven of proposed labeling (Attachment 1 of the submission) under "Activation of Mania/Hypomania" it is recommended that the sponsor change the highlighted sentence "One additional case of hypomania has been reported ... treatment" to the following (to reflect that the event occurred in controlled [redacted] trials):

[ ]

- Proposed modification in Table 4 on page 20 of proposed labeling in Attachment 1 of the submission is noted (in response to requests to update this table to incorporate results from the GAD trials in submission S-003). However, the results supporting these updated changes cannot be found in the submission and should be provided.

Finally, see previous reviews for S-003, for the original NDA and for subsequent NDA submissions for labeling recommendations relevant to special populations at risk for bradycardia and QT prolongation. Dr. Andreason notes in his 8/27/03 Memo to the File for the original S-003 submission, that the Division Safety Group is currently examining this issue.

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

cc: IND
HFD 120
HFD 120/P Andreason, K Brugge, R. Taylor, T Laughren, L Rocca

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 27, 2003

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Escitalopram in the treatment of Generalized Anxiety Disorder

TO: File, NDA 21-323 SE1-003 and NDA 21-365 SE1-004
[Note: This memo should be filed with the November 26, 2002 original submission of this NDA.]

1.0 Background

Escitalopram (s-citalopram) is the active enantiomer of citalopram, which is a racemic mixture of the R and S forms. Citalopram and Escitalopram are approved for the treatment of Major Depressive Disorder. Though other SSRIs are indicated for a myriad of the anxiety disorders (e.g. Social Anxiety Disorder, Panic Disorder, Obsessive Compulsive Disorder, Post-traumatic Stress Disorder), only paroxetine among the SSRIs is approved for the treatment of GAD.

This efficacy supplement offers the results of three clinical trials in the support of escitalopram for the treatment of Generalized Anxiety Disorder. These studies were MD-05, MD-06, and MD-07. All three were 8-week, randomized, double blind, placebo controlled, parallel group, and flexible dose studies of escitalopram 10-20-mg/day (single dose) in the treatment of adult patients with DSM-IV Generalized Anxiety Disorder.

2.0 Chemistry

Escitalopram is a marketed drug product. Only currently marketed forms were used in the clinical trials. There are no CMC related changes in labeling with this supplement.

3.0 Pharmacology/Toxicology

Escitalopram is a currently marketed drug product. There were no pre-clinical pharmacology/ toxicology review issues related to this supplement.

4.0 Biopharmaceutics

OCPB consultation with this supplement was not necessary since patients with GAD are not expected to metabolize escitalopram differently than patients with Major Depressive Disorder.

5.0 Clinical Data

This efficacy supplement offers the results of three clinical trials in the support of escitalopram for the treatment of Generalized Anxiety Disorder. These studies were MD-05, MD-06, and MD-07. All

three identically designed studies were 8-week, randomized, double blind, placebo controlled, parallel group, and flexible dose studies of escitalopram 10-20-mg/day (single dose) in the treatment of adult patients with DSM-IV Generalized Anxiety Disorder. Karen Brugge, MD was the primary clinical reviewer for this supplement. She found that the data were adequate to reach a conclusion on this review. The following table from Dr Brugge's review summarizes the three trials.

Clinical Studies of Escitalopram for GAD

Protocol No	Study Design	Treatment Groups	N (Randomized) per Treatment group	N (Completers) per Treatment group (% of ITT Efficacy Pop.*)	N (ITT Efficacy Pop.) * per Treatment group	N (ITT Safety Pop.) ** per Treatment group
SCT-MD-05	Multicenter, Double blind,	Placebo group	128	95 (74%)	128	128
8-Week GAD* Trial**	Randomized, Flexible dose, Parallel group	10-20 mg/day SCT	129 **Total: 257**	97 (77%) **Total: 192**	124 **Total: 252**	126 **Total: 254**
	25 U.S. sites****					
SCT-MD-06	Multicenter, Double blind,	Placebo group	145	114 (80%)	138	142
8-Week GAD* Trial**	Randomized, Flexible dose, Parallel group	10-20 mg/day SCT	149 **Total: 294**	118 (81%) **Total: 232**	143 **Total: 281**	145 **Total: 287**
	19 U.S. sites****					
SCT-MD-07	Multicenter, Double blind,	Placebo group	159	123 (78%)	153	157
8-Week GAD* Trial**	Randomized, Flexible dose, Parallel group	10-20 mg/day SCT	161 **Total: 320**	119 (75 %) **Total: 242**	154 **Total: 307**	158 **Total: 315**
	23 US sites****					
		Grand Totals:	**N=871**	**N=666**	**N=840**	**N=856**

*ITT Efficacy population: randomized subjects having at least one dose of double blind study drug and at least one post-baseline Hamilton Anxiety Rating Scale assessment.
**ITT Safety Population: randomized subjects having at least one dose of double blind study drug.
***GAD = Generalized Anxiety disorder
**** Only sites with randomized subjects are enumerated in this table.

The primary efficacy variable for all studies was the 14-item Hamilton Anxiety Scale (HAM-A) via Last Observation Carried Forward (LOCF) method. All studies showed a statistically significant ($p<0.05$) improvement over placebo with respect to the HAM-A. Biometrics review by Kun He validated the Sponsor's protocol defined analysis of the study data. The Observed Case analysis that I note in the table below was not protocol specified but is included as confirmatory evidence of efficacy.

ANCOVA for Change of HAM-A (LOCF)

	Placebo		Escitalopram		P-value
	(Mean	SE)	(Mean	SE)	
SCT-MD-05	-7.7	0.6	-9.6	0.6	.044
SCT-MD-06	-7.6	0.5	-9.2	0.5	.032
SCT-MD-07	-7.4	0.6	-11.3	0.6	<.0001

ANCOVA for Change of HAM-A (OC)

	Placebo		Escitalopram		P-value
	(Mean	SE)	(Mean	SE)	
SCT-MD-05	-8.6	0.6	-10.5	0.6	.176
SCT-MD-06	-8.0	0.6	-9.8	0.6	.007
SCT-MD-07	-8.2	0.6	-12.9	0.6	<.0001

* From Tables 3.1.6.1 and 3.1.6.2 .from Biometrics review by Kun He

There were no pre-determined key secondary efficacy variables; however, the sponsor had several secondary variables that they wished to explore for reasons other than product labeling. Analyses of these secondary variables revealed similar results with respect to superior reduction of anxiety symptoms in escitalopram treated patients versus placebo treated patients. Gender effects on efficacy were not observed; there were insufficient numbers of patients to adequately assess age or race differences in efficacy.

Dr. Brugge and Kun He noted in their reviews that if one removes the most positive sites from each of the studies, study MD-07 remains positive ($p<0.0001$) but studies MD-06 and MD-05 fail at ($p=0.06$ and 0.15) respectively. Dr. Brugge recommended that these two sites be chosen for the DSI investigation. Reports from investigations of the MD-06 site showed that data was acceptable. Therefore, there are at least two positive studies supporting efficacy for the use of escitalopram for the treatment of Generalized Anxiety Disorder and though MD-05 site investigation is pending, from a review standpoint the results are moot.

An analysis of the HAM-D revealed an overall improvement in depressive symptomatology in this sample of Generalized Anxiety Disorder patients. There were no completed or attempted suicides in the controlled trial data. There was one completed suicide in the extension study MD-17 (Patient 5078 on day 126) and a suicide attempt (patient 7187 on day 30). It appears that both of these cases were due to underlying psychopathology as opposed to some kind of idiosyncratic drug related adverse event. Drug induced worsening of depression or increase in suicidal behavior was not seen in this sample of Generalized Anxiety Disorder patients.

There was no compelling evidence in this submission for discontinuation emergent adverse events (withdrawal); however, withdrawal was not systematically studied and therefore I recommend that labeling remain silent on this lack-of-finding.

I agree with Dr. Brugge's recommendation that the Division take an Approvable (AE) action on Supplement 003 indicating Lexapro® for the treatment of GAD. This AE action may proceed to approval based on final agreement on labeling and presentation of additional data outlined in the attached AE action letter.

- Subject 1532 (study 99269) was reported as having a seizure. The subject was a 28 year old female with a history of a seizure at 6 years old. Labeling already includes a precautionary statement regarding patients with a history of seizures. In a 3/12/03- amendment to the submission that included some updated information, the study drug in S1532 was unblinded and found to be escitalopram. I recommend that this subject is counted among subjects having seizures, as described under the "Precautions" section of labeling.
- Subject 1184 had hypomania on blinded drug (Study 99269). This subject was described in a later amendment to the submission as having received escitalopram. Therefore, the section on mania under "Precautions" should be updated to include this patient in the enumeration of induction of mania/hypomania cases.
- [redacted]

Pending Safety Group labeling issues:

- The Safety Group is conducting a consultative review at the time of this writing, based on a Clinical review of the 11/12/02 NDA 21-323 and in light of an Office of Drug Safety (ODS) recommendation for the following labeling change:

  It would be prudent to advise caution in prescribing citalopram to patients with risk factors for developing QT prolongation and ventricular arrhythmia [ ]

- Dr. Brugge notes that one patient (2374) reported a serious adverse event of "stomach ulcer and hemorrhage" who was not taking a non-steroidal anti-inflammatory agent. This patient had a positive history of peptic ulcer disease. Another escitalopram patient (3188) had alcohol abuse disorder and was believed to have been actively consuming alcohol whereby he had a series of events of gastritis and hematemesis. These were the only two patients with SAEs involving upper GI bleed out of 2552 escitalopram and 816 citalopram subjects. Class labeling for SSRI associated abnormal bleeding events is currently under negotiation with all of the SSRI Sponsors.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Andreason
8/27/03 02:05:41 PM
MEDICAL OFFICER

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: December 15, 2003

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation of Approval Action for 21-323 SE1-003 (oral tablet formulation)
21-365 SE1-004 (oral solution formulation)

TO: File, NDA 21-323 and NDA 21-365
[Note: This memo should be filed with the October 20, 2003 submissions to these NDAs.]

The labeling changes indicated in the 9/26/03 Action Letter were accepted by the sponsor and sections to the draft labeling were updated upon our request. There were 4 cases of convulsion that were noted by the Safety Team in patients treated with escitalopram as opposed top the one case that was reported in the Generalized Anxiety Disorder submission reviewed by Dr. Brugge; this has also been incorporated into the labeling that is attached to this approval action package.

Since the time of our Approvable Action letter of 9/26/03 the Division has completed its review of bleeding related adverse events (BRAE) and discontinuation syndrome draft labeling language. This new language is currently being disseminated to sponsors of the applicable drugs. I note that the labeling that we attaché to the action package includes the BRAE and discontinuation syndrome language.

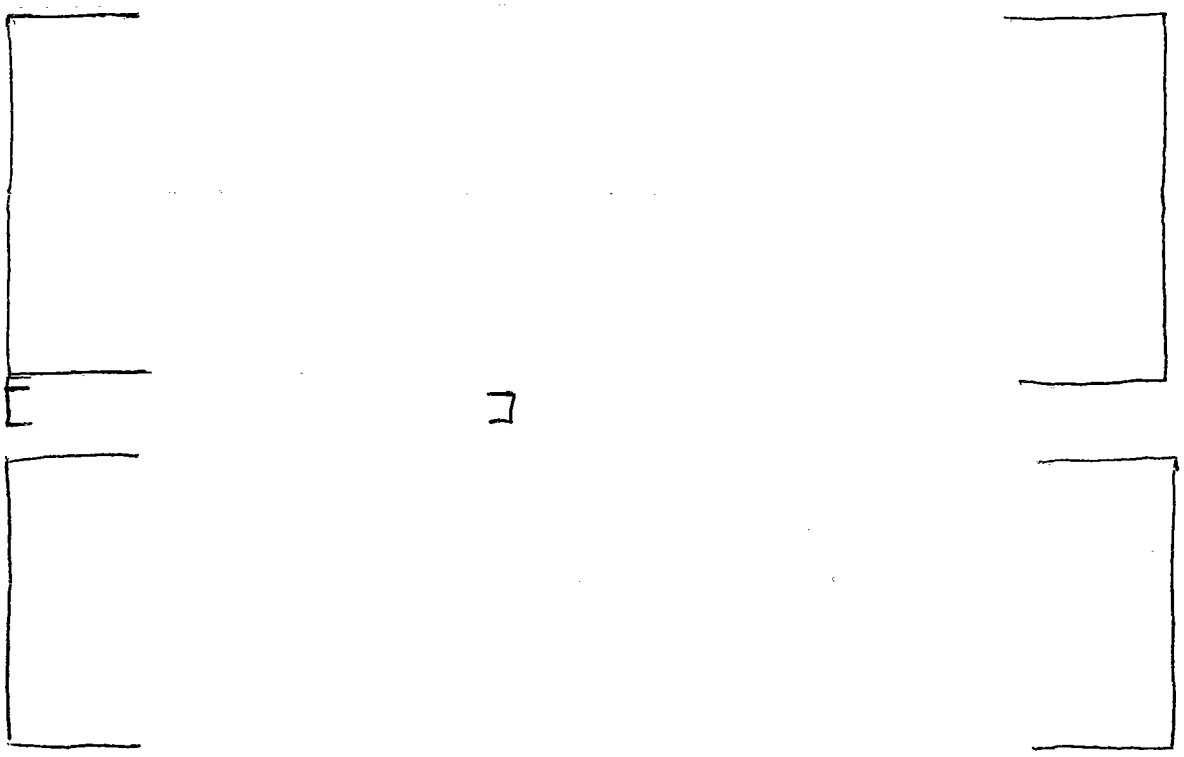
In the following paragraphs I respond to Dr. Brugge's comments in her review of the Response to Approvable letter. In her review Dr. Brugge stated:

> 1. It is recommended that the sponsor provide additional information on the following subjects (e.g. results of diagnostic and other clinical assessments, presence of underlying illness and risk factors, and complete medication and study drug information, that would help to determine the etiology of the events:
>
> a. Two subjects diagnosed with pulmonary embolism (subject 129 in protocol 99812 and subject 8041 who was described in the original submission on SAEs in "Other Trials").
>
> b. Two subjects with life-threatening gastrointestinal events requiring surgical interventions (subject 002903 in Study MD-12 and subject 166-1 in study 99862).

Team Leader comment: It is reasonable to have the sponsor provide additional information on the four cases to which Dr Brugge refers; however, I do not believe that getting more information on these cases should delay our action at this point. Our

proposed language for bleeding-related-adverse-events provides for warnings that encompass the case of gastric resection due to the ulcer. The other cases will be discussed with the Office of Drug Safety, but in my opinion, do not warrant delaying an action at this time.

2. It is recommended that the Office of Drug Safety (which is currently reviewing postmarketing data for a potential signal of seizures associated with citalopram) is made aware of events of seizures reported with escitalopram, including subject S1005 in study 99769. Furthermore, additional information on this subject should be obtained that may shed light on the etiology of the event (results of diagnostic tests and other relevant clinical assessments, among other clinical information that may be useful in determining the etiology). Given the information available at this time, the sponsor's update in the section on "Seizures" (page 7 of their proposed labeling) is reasonable.
Team Leader comment: This can be accomplished by copying Dr. Brugge's review to ODS. Additionally this adverse event is being followed by out Safety Team.



5. An OCPB consult is recommended regarding the [two] case reports of a potential citalopram-linezolid interaction resulting in development of serotonin syndrome with regards to escitalopram, citalopram labeling and potentially for Zyvox. labeling. It is noted that approved labeling for Zyvox. indicates the following under Drug-Drug Interactions:

> *"Serotonergic Agents:* The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20-mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan. The effects of other serotonin re-uptake inhibitors have not been studied."

Team Leader Comment: I disagree that a consult from OCPB is needed to place language in labeling warning against [ ] of escitalopram and linezolid. Linezolid is

already recognized as a reversible MAO inhibitor. I recommend that this drug interaction be added to the Warning Section of labeling and that the two case reports along with a notice of our decision to place this information in labeling be forwarded to the reviewing Division for linezolid. [ ]

[ ]

6. The following are recommendations regarding sections of labeling that were modified by the sponsor in response to our request indicated in the Approvable Letter: On page seven of proposed labeling (Attachment 1 of the submission) under "Activation of Mania/Hypomania" it is recommended that the sponsor change the highlighted sentence "One additional case of hypomania has been reported ... treatment" to the following (to reflect that the event occurred in controlled [ ] trials):

[ ]

Proposed modification in Table 4 on page 20 of proposed labeling in Attachment 1 of the submission is noted (in response to requests to update this table to incorporate results from the GAD trials in submission S-003). However, the results supporting these updated changes cannot be found in the submission and should be provided. Finally, see previous reviews for S-003, for the original NDA and for subsequent NDA submissions for labeling recommendations relevant to special populations at risk for bradycardia and QT prolongation. Dr. Andreason notes in his 8/27/03 Memo to the File for the original S-003 submission, that the Division Safety Group is currently examining this issue.

[ ]

Recommendations and Conclusions

Labeling is attached to this action package that was negotiated and agreed upon by the Sponsor and the Division. The sponsor has fairly responded to all of the points in the Approvable Action letter. I therefore recommend that the Division take an Approval action on supplements 21-323 SE1-003 (oral tablet formulation) and 21-365 SE1-004 (oral solution formulation).

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/s/

Paul Andreason
12/15/03 08:37:20 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

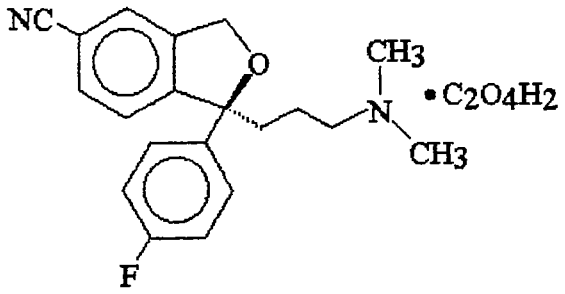
21-323/S-003 & 21-365/S-004

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA Number: **21-323**
3. SUPPLEMENT NUMBERS/DATES: **SE1-003**
   Letter date: November 26, 2002
   Stamp date: November 27, 2002
4. AMENDMENTS/REPORTS/DATES:
   Letter date: July 11, 2003
   Stamp date: July 14, 2003
5. RECEIVED BY CHEMIST: December 10, 2002
6. APPLICANT NAME & ADDRESS: Forest Laboratories, Inc.
   Harborside Financial Center
   Plaza Three, Suite 602
   Jersey City, New Jersey 07311
7. NAME OF DRUG: Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg, 20 mg
8. NONPROPRIETARY NAME: Escitalopram oxalate
9. CHEMICAL NAME/STRUCTURE: S (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobezofuran-5-carbonitrile, hydrogen oxalate

   MW: 414.42, $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$



10. DOSAGE FORM(S): Coated Tablet
11. POTENCY: 5 mg, 10 mg, 20 mg
12. PHARMACOLOGICAL CATEGORY: Antidepressant
13. HOW DISPENSED: X (R_x) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No
    REVIEW RECORDS & REPORTS CURRENT X Yes _____ No
15. RELATED IND/NDA/DMF: NA

16. SUPPLEMENT PROVIDES FOR: The use of Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg and 20 mg for the new indication, Generalized Anxiety Disorder (GAD).

17. COMMENTS:
Concerning Forest Laboratories supplement application for Lexapro™ (escitalopram oxalate) Tablets for the new indication of generalized anxiety disorder (GAD), the sponsor believes FDA approval of this supplement will not significantly increase the use of the active moiety. Therefore, Forest Laboratories claims categorical exclusion from environmental assessment under 21 CFR 25.31(b). In addition, the sponsor certifies that to their knowledge no extraordinary circumstances exist as per 21 CFR 25.15(d).

On July 2, 2003 Lorenzo Rocca, Ph.D. (HFD-120) contacted by telephone John A. Baiano, Ph.D., Regulatory Affairs, Forest Laboratories in order to confirm that when performing the safety and efficacy studies of Lexapro™ (escitalopram oxalate) Tablets in the treatment of GAD, Forest Laboratories used the approved drug product. On July 11, 2003 Forest Laboratories submitted supplemental amendment 21-323/SE8-

007(BC) in response to the July 2, 2003 telephone conversation. The July 11, 2003 supplemental amendment includes the follow statement addressing the FDA's question concerning the nature of the drug product used by Forest in their safety and efficacy studies involving treatment of GAD:

...all CMC changes since the approval of the original Lexapro™ Tablets NDA (NDA 21-323 approved on 8/14/02, for Major Depressive Disorder) and the original Lexapro™ Oral Solution NDA (NDA 21-365 approved on 11/27/02, for Major Depressive Disorder) have been appropriately filed as supplements and/or amendments to the respective NDAs.

Based on the above statement, it is reasonable to conclude that no CMC changes were made to the drug product used by Forest Laboratories in their safety and efficacy studies involving the use of Lexapro™ (escitalopram oxalate) Tablets, 5 mg, 10 mg, 20 mg in the treatment of GAD.

18. CONCLUSIONS & RECOMMENDATIONS: Recommend issuing approval letter.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca	_____	_____
20. TEAM LEADER NAME	SIGNATURE	DATE COMPLETED
Thomas F. Oliver	_____	_____

cc:
NDA 21-323/SE1-003
HFD-120/Division File
HFD-120/TOliver
HFD-120/LRocca
HFD-120/PDavid

F/T by: LRocca, File: C:Data\LR\Supplement\n21323\SE1003\SE1-003Review1.doc

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/s/

Lorenzo Rocca
8/8/03 12:37:29 PM
CHEMIST

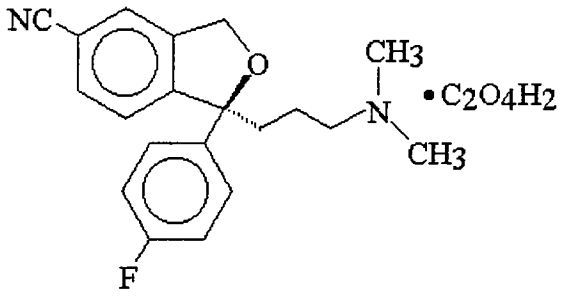
Thomas Oliver
8/8/03 01:02:15 PM
CHEMIST

CHEMIST REVIEW
OF **SUPPLEMENT 2**

1. ORGANIZATION: HFD-120
2. NDA Number: **21-323**
3. SUPPLEMENT NUMBERS/DATES: **SE1-003**
   Letter date: November 26, 2002
   Stamp date: November 27, 2002
4. AMENDMENTS/REPORTS/DATES:
   Letter date: July 11, 2003
   Stamp date: July 14, 2003
5. RECEIVED BY CHEMIST: December 10, 2002

6. APPLICANT NAME & ADDRESS: Forest Laboratories, Inc.
   Harborside Financial Center
   Plaza Three, Suite 602
   Jersey City, New Jersey 07311
7. NAME OF DRUG: Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg, 20 mg
8. NONPROPRIETARY NAME: Escitalopram oxalate
9. CHEMICAL NAME/STRUCTURE: S (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobezofuran-5-carbonitrile, hydrogen oxalate

   MW: 414.42, $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$



10. DOSAGE FORM(S): Coated Tablet
11. POTENCY: 5 mg, 10 mg, 20 mg
12. PHARMACOLOGICAL CATEGORY: Antidepressant
13. HOW DISPENSED: X (R_x) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No
    REVIEW RECORDS & REPORTS CURRENT X Yes _____ No
15. RELATED IND/NDA/DMF: NA

16. SUPPLEMENT PROVIDES FOR: The use of Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg and 20 mg for the new indication, Generalized Anxiety Disorder (GAD).

17. COMMENTS:
Concerning Forest Laboratories supplement application for Lexapro™ (escitalopram oxalate) Tablets for the new indication of generalized anxiety disorder (GAD), the sponsor believes FDA approval of this supplement will not significantly increase the use of the active moiety. Therefore, Forest Laboratories claims categorical exclusion from environmental assessment under 21 CFR 25.31(b). In addition, the sponsor certifies that to their knowledge no extraordinary circumstances exist as per 21 CFR 25.15(d).

On July 2, 2003 Lorenzo Rocca, Ph.D. (HFD-120) contacted by telephone John A. Baiano, Ph.D., Regulatory Affairs, Forest Laboratories in order to confirm that when performing the safety and efficacy studies of Lexapro™ (escitalopram oxalate) Tablets in the treatment of GAD, Forest Laboratories used the approved drug product. On July 11, 2003 Forest Laboratories submitted supplemental amendment 21-323/SE8-

007(BC) in response to the July 2, 2003 telephone conversation. The July 11, 2003 supplemental amendment included the follow statement addressing the FDA's question concerning the nature of the drug product used by Forest in their safety and efficacy studies involving treatment of GAD:

...all CMC changes since the approval of the original Lexapro™ Tablets NDA (NDA 21-323 approved on 8/14/02, for Major Depressive Disorder) and the original Lexapro™ Oral Solution NDA (NDA 21-365 approved on 11/27/02, for Major Depressive Disorder) have been appropriately filed as supplements and/or amendments to the respective NDAs.

Based on the above statement, it was concluded (see 21-323/SE1-003 Chemistry Review 1, Lorenzo Rocca, Ph.D. approved July 8, 2003) that no CMC changes were made to the drug product used by Forest Laboratories in their safety and efficacy studies involving Lexapro™ (escitalopram oxalate) Tablets, 5 mg, 10 mg, 20 mg in the treatment of GAD. However, it was determined at a later date that the formulation, used in the sponsor's efficacy trials supporting the approval of escitalopram oxalate for the indication of GAD, was as follows (see Review and Evaluation of Clinical Date, Karen L. Brugge, M.D., approved August 27, 2003):

- 10 mg and 20 mg encapsulated escitalopram oxalate tablets (also 20 and 40 mg citalopram encapsulated tablets and placebo were employed).

The sponsor therefore will be asked to address the following chemistry issues, and until the sponsor has adequately addressed these issues the original recommendation issued with 21-323/SE1-003 Chemistry Review 1 should be ignored.

1) Please describe in detail the over encapsulated Lexapro™ (escitalopram oxalate) Tablet formulation 10 mg, 20 mg, encapsulated Celexa™ (citalopram HBr) 20 mg and 40 mg and the Placebo Capsule formulation used in the efficacy trials for GAD. Please include a detailed description of the capsule shell (i.e., size, color, manufacturer, and acceptance testing (methods and specifications)), and a detailed description of the materials used to fill the clinical capsule formulation.
2) Please provide dissolution results (i.e., dissolution plots and f2 calculations) demonstrating that the encapsulated Lexapro™ (escitalopram oxalate) Tablet formulation 10 mg, 20 mg and the encapsulated Celexa™ (citalopram HBr) Tablet formulation 20 mg, 40 mg releases drug in a manner which is identical to the approved drug products.

18. CONCLUSIONS & RECOMMENDATIONS: Until the sponsor has adequately responded to the two chemistry issues listed above, NDA 21-323/SE1-003 is approvable for CMC.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca		

20. TEAM LEADER NAME	SIGNATURE	DATE COMPLETED
Thomas F. Oliver		

cc:
NDA 21-323/SE1-003
HFD-120/Division File
HFD-120/TOliver
HFD-120/GGill-Sangha
HFD-120/LRocca
HFD-120/AMHomonnay-Weikel

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/s/

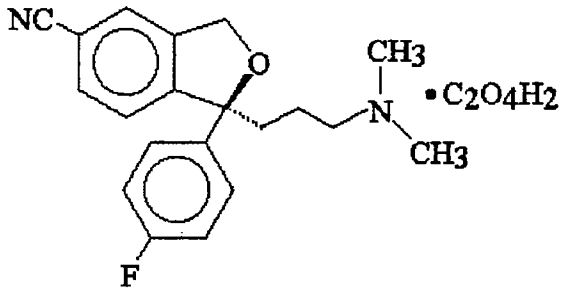
Lorenzo Rocca
9/24/03 09:57:19 AM
CHEMIST
This review is the second CMC review of 21-323/SE1-003. The first review is dated 7/8/03. The approvable recommendation for this review replaces the approval recommendation for the first review.

Gurpreet Gill-Sangha
9/24/03 10:01:23 AM
CHEMIST
Acting for Thomas Oliver

CHEMIST REVIEW
OF **SUPPLEMENT 3**

1. ORGANIZATION: HFD-120
2. NDA Number: **21-323**
3. SUPPLEMENT NUMBERS/DATES: **SE1-003**
   Letter date: November 26, 2002
   Stamp date: November 27, 2002
4. AMENDMENTS/REPORTS/DATES: SE1-003(BZ)
   Letter date: October 20, 2003
   Stamp date: October 21, 2003
5. RECEIVED BY CHEMIST: December 10, 2002
6. APPLICANT NAME & ADDRESS: Forest Laboratories, Inc.
   Harborside Financial Center
   Plaza Three, Suite 602
   Jersey City, New Jersey 07311
7. NAME OF DRUG: Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg, 20 mg
8. NONPROPRIETARY NAME: Escitalopram oxalate
9. CHEMICAL NAME/STRUCTURE: S (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobezofuran-5-carbonitrile, hydrogen oxalate

   MW: 414.42, $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$



10. DOSAGE FORM(S): Coated Tablet
11. POTENCY: 5 mg, 10 mg, 20 mg
12. PHARMACOLOGICAL CATEGORY: Antidepressant
13. HOW DISPENSED: X (Rx) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No
    REVIEW RECORDS & REPORTS CURRENT X Yes _____ No
15. RELATED IND/NDA/DMF: NA

16. SUPPLEMENT PROVIDES FOR: The use of Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg and 20 mg for the new indication, Generalized Anxiety Disorder (GAD).

17. COMMENTS:
    The sponsor in their October 20, 2003 letter to the FDA titled *Response to FDA Approvable Letter: Generalize Anxiety Disorder (GAD)* (NDA 21-323/SE1-003(BZ), October 20, 2003) has adequately addressed all chemistry issues.

18. CONCLUSIONS & RECOMMENDATIONS: Recommend issuing approval letter.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca		

20. TEAM LEADER NAME	SIGNATURE	DATE COMPLETED
Thomas F. Oliver		

cc:
NDA 21-323/SE1-003
HFD-120/Division File
HFD-120/TOliver
HFD-120/LRocca
HFD-120/STaylorl

F/T by: LRocca, File: C:Data\LR\Supplement\n21323\SE1003\SE1-003Review3.doc

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/s/

Lorenzo Rocca
10/31/03 11:18:54 AM
CHEMIST

Thomas Oliver
11/3/03 08:55:38 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-003 & 21-365/S-004

STATISTICAL REVIEW(S)

TYPOGRAPHICAL ERROR

Statistical Review-
"20-505 & 20-844" is a typographical error. Should state "21-323 & 21-365."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-323/SE1-003
Drug Name:	Lexapro ® (escitalopram oxalate)
Indication:	Generalized anxiety disorder (GAD)
Sponsor:	Forest Laboratories
Date:	11/26/2002
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD 710)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Kun Jin, , Ph.D.,Team Leader George Chi, Ph.D., Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
Clinical Team:	Karen Brugge, M.D., Ph.D., Clinical Reviewer Thomas Laughren, M.D., Team Leader Russell Katz, M.D., Director
Project Manager:	Annie Homonnay-Weikel, R. Ph.

Keywords: ANOVA, generalized anxiety disorder, lexapro

TABLE OF CONTENTS

Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

Three studies showed that escitalopram group had greater mean change from baseline to Week 8 in HAMA than placebo group. The analyses are nominally statistically significant. But one should interpret the results with caution since the findings might not be robust.

1.2 Brief Overview of Clinical Studies

There are three studies in the submission. Each study was a randomized, double-blind, placebo-controlled, multicenter, parallel-group, and flexible dose. All studies were conducted in USA. Each study consisted of a one-week single-blind placebo lead-in period, followed by an eight-week double-blind treatment period. At the end of the single-blind period, patients between 18 to 80 years of age meeting DSM-IV criteria for GAD were to be randomized to one of two double-blind treatment groups (escitalopram or placebo). The initial dose of escitalopram was 10 mg/day, with a possible increase to 20 mg/day after 4 weeks. The primary endpoint is change from baseline to Week 8 in Hamilton Anxiety Scale (HAMA), and the primary analysis is ANCOVA with terms for treatment, center, and baseline as covariate.

SCT-MD-05 had 25 centers whose ITT population had 128 in placebo, and 124 in escitalopram groups, respectively. SCT-MD-06 had 19 centers whose ITT population had 138 in placebo, and 143 in escitalopram groups, respectively. SCT-MD-07 had 23 centers whose ITT population had 153 in placebo, and 154 in escitalopram groups, respectively.

1.3 Statistical Issues and Findings

There were large percentages of negative centers in SCT-MD-05 (36%) and SCT-MD-06 (37%). The results are very sensitive to centers. In SCT-MD-05 if Center 01 with 3 patients total (2 in placebo, and 1 in escitalopram) is removed due to nonrobust center effect size, the result would not be statistically nominally significant any more. In SCT-MD-06, if Center 05 with 11 patients total (5 in placebo, and 6 in escitalopram) is removed due to nonconsistent center effect size the result would not be statistically nominally significant any more. One should interpret the results with caution since the findings might not be robust.

2. Introduction

2.1 Overview

Generalized anxiety disorder (GAD) is a common psychiatric illness that affects approximately 2.8% of the adult US population each year. Escitalopram (Lu 26-054) is a selective serotonin reuptake inhibitor (SSRI) that is approved for the treatment of major depressive disorder in the US and for the treatment of depression and panic disorder in countries outside the US. The evaluation of the efficacy of escitalopram in the treatment of GAD is based on three trials (Studies SCT-MD-05, SCT-MD-06, and SCT-MD-07) conducted in outpatients with a diagnosis of GAD.

2.2 Data Sources

Hard copy of volumes 1 to 62.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Objective of Studies SCT-MD-05, SCT-MD-06, and SCT-MD-07

The objective of each study was to compare the safety and efficacy of escitalopram to placebo in the treatment of GAD.

3.1.2 Study Design

Each study was a randomized, double-blind, placebo-controlled, multicenter, parallel-group, and flexible dose. Each study consisted of a one-week single-blind placebo lead-in period, followed by an eight-week double-blind treatment period. At the end of the single-blind period, patients between 18 to 80 years of age meeting DSM-IV criteria for GAD were to be randomized to one of two double-blind treatment groups (escitalopram or placebo). The initial dose of escitalopram was 10 mg/day, with a possible increase to 20 mg/day after 4 weeks. The primary efficacy variable Hamilton Anxiety Scale (HAMA) was measured at screen, baseline, and weeks 1, 2, 4, 6, and 8 of double-blind treatment period.

3.1.3 Efficacy Measures

The primary efficacy endpoint was change from baseline to Week 8 in the Hamilton Anxiety Scale (HAMA), which is a 14-item scale rated the patient's level of anxiety. Each item was scored on a 5-point scale with 0 reflecting no symptoms and 4 reflecting symptoms of maximum severity. A minimum of 18 on the total score, and a minimum of 2 on the tension and anxiety items were required for study inclusion.

Secondary efficacy measures include HAMA Psychic Anxiety Subscale, and Clinical Global Impressions (CGI).

3.1.4 Statistical Analysis Plan

All primary analyses would be performed using the Last Observation Carried Forward (LOCF) approach based on the Intent-to-treat (ITT) population.

The primary analysis was ANCOVA with terms for treatment, center, and treatment by center interaction as the factors and baseline score as covariate. The additive model would be used if the interaction term was not significant.

In an Octobor 1, 2001 response to comments from the Office of Biometrics, Forest clarified that treatment efficacy would be evaluated using an additive ANCOVA model with treatment and center as factors and baseline score as covariate (without the treatment-by-center interaction term) and consistency of treatment efficacy across centers would be examined graphically.

3.1.5 Study Population

For Study SCT-MD-05, a total of 257 patients (128 in placebo, and 129 in escitalopram) were randomized. There were 3 in escitalopram group who didn't receive study drug, and 2 who had no post-baseline HAMA assessment. A total of 254 (128 in placebo, and 124 in escitalopram) formed the ITT population. The following table (adapted from Study report vol.2, p52) presents the patient disposition information.

SCT-MD-05: Patient Disposition and Reasons for Discontinuation

	Placebo (N=128)	*Escitalopram (N=126)*	*Total (N=254)*
Total Completers	95 (74.2)	97 (77.0)	192 (75.6)
Total Withdrawn for Any Reason	33 (25.8)	29 (23.0)	62 (24.4)
Adverse Event	4 (3.1)	14 (11.1)	18 (7.1)
Withdrawal of Consent	10 (7.8)	7 (5.6)	17 (6.7)
Lost to Follow-Up	8 (6.3)	4 (3.2)	12 (4.7)
Insufficient Therapeutic Response	8 (6.3)	2 (1.6)	10 (3.9)
Protocol Violation	3 (2.3)	1 (0.8)	4 (1.6)
Other	0	1 (0.8)	1 (0.4)

Safety Population
Cross reference: Table 1.2.

For Study SCT-MD-06, a total of 294 patients (145 in placebo, and 149 in escitalopram) were randomized. There were 3 who didn't receive study drug, and 4 who had no post-baseline HAMA assessment in placebo group, and 4 who didn't receive study drug, and 2 who had no post-baseline HAMA assessment in escitalopram group, respectively. A total of 281 (138 in placebo, and 143 in escitalopram) formed the ITT population. The following table (adapted from Study report vol.16, p50) presents the patient disposition information.

SCT-MD-06: Patient Disposition and Reasons for Discontinuation

	Placebo (N=142)	*Escitalopram (N=145)*	*Total (N=287)*
Total Completers	114 (80.3)	118 (81.4)	232 (80.8)
Total Withdrawn for Any Reason	28 (19.7)	27 (18.6)	55 (19.2)
Adverse Event	3 (2.1)	8 (5.5)	11 (3.8)
Lost to Follow-Up	10 (7.0)	7 (4.8)	17 (5.9)
Withdrawal of Consent	11 (7.7)	5 (3.4)	16 (5.6)
Insufficient Therapeutic Response	0	4 (2.8)	4 (1.4)
Protocol Violation	2 (1.4)	2 (1.4)	4 (1.4)
Other	2 (1.4)	1 (0.7)	3 (1.0)

Safety Population
Cross reference: Table 1.2.

For Study SCT-MD-07, a total of 320 patients (159 in placebo, and 161 in escitalopram) were randomized. There were 2 who didn't receive study drug, and 4 who had no post-baseline HAMA assessment in placebo group, and 3 who didn't receive study drug, and 4 who had no post-baseline HAMA assessment in escitalopram group, respectively. A total of 307 (153 in placebo, and 154 in escitalopram) formed the ITT population. The following table (adapted from Study report vol.28, p50) presents the patient disposition information.

SCT-MD-07: Patient Disposition and Reasons for Discontinuation

	Placebo (N=157)	*Escitalopram (N=158)*	*Total (N=315)*
Total Completers	123 (78.3)	119 (75.3)	242 (76.8)
Total Withdrawn for Any Reason	34 (21.7)	39 (24.7)	73 (23.2)
Adverse Event	8 (5.1)	14 (8.9)	22 (7.0)
Lost to Follow-Up	12 (7.6)	12 (7.6)	24 (7.6)
Withdrawal of Consent	6 (3.8)	6 (3.8)	12 (3.8)
Insufficient Therapeutic Response	5 (3.2)	2 (1.3)	7 (2.2)
Protocol Violation	3 (1.9)	4 (2.5)	7 (2.2)
Other	0	1 (0.6)	1 (0.3)

Safety Population
Cross reference: Table 1.2.

For Study SCT-MD-05, next two tables present the information of demographic characteristics (vol. 2, p54) and efficacy parameter at baseline (vol.2, p55).

SCT-MD-05: Demographic Characteristics

characteristic		Placebo (N=128)	Escitalopram (N=126)
Age (years)	Mean (SD) range	40.9 (14.0) 18-74	39.6 (13.4) 18-79
Sex, n (%)	Female Male	80 (62.5) 48 (37.5)	75 (59.5) 51 (40.5)
Race, n (%)	Caucasian Non-Caucasian	116 (90.6) 12 (9.4)	111 (88.1) 15 (11.9)
Weight (lbs)	Mean (SD) range	168.4 (37.9) 85-270	178.4 (46.9) 100-350

SCT-MD-05: Efficacy Parameter at Baseline (Mean ± SE)

Parameter	Placebo (N=128)	Escitalopram (N=124)
HAMA	22.1 ± 0.3	22.8 ± 0.3
HAMA psychic anxiety subscale	13.1 ± 0.2	13.1 ± 0.2
CGI-S	4.2 ± 0.05	4.3 ± 0.04

For Study SCT-MD-06, next two tables present the information of demographic characteristics (vol. 16, p52) and efficacy parameter at baseline (vol.16, p53).

SCT-MD-06: Demographic Characteristics

characteristic		Placebo (N=142)	Escitalopram (N=145)
Age (years)	Mean (SD) range	38.6 (12.5) 18-73	36.8 (12.2) 18-65
Sex, n (%)	Female Male	69 (48.6) 73 (51.4)	89 (61.4) 56 (38.6)
Race, n (%)	Caucasian Non-Caucasian	110 (77.5) 32 (22.5)	113 (77.9) 32 (22.1)
Weight (lbs)	Mean (SD) range	172.1 (43.1) 109-335	163.0 (38.0) 95-315

SCT-MD-06: Efficacy Parameter at Baseline (Mean ± SE)

Parameter	Placebo (N=138)	Escitalopram (N=143)
HAMA	22.6 ± 0.3	22.6 ± 0.3
HAMA psychic anxiety subscale	13.0 ± 0.2	13.5 ± 0.2
CGI-S	4.3 ± 0.04	4.3 ± 0.04

For Study SCT-MD-07, next two tables present the information of demographic characteristics (vol. 28, p52) and efficacy parameter at baseline (vol.28, p53).

SCT-MD-07: Demographic Characteristics

characteristic		Placebo (N=157)	Escitalopram (N=158)
Age (years)	Mean (SD) range	39.5 (13.1) 18-78	39.5 (12.1) 19-76
Sex, n (%)	Female Male	83 (52.9) 74 (47.1)	83 (52.5) 75 (47.5)
Race, n (%)	Caucasian Non-Caucasian	112 (71.3) 45 (28.7)	112 (70.9) 46 (29.1)
Weight (lbs)	Mean (SD) range	173.9 (46.5) 88-359	172.3(42.1) 96-305

SCT-MD-07: Efficacy Parameter at Baseline (Mean ± SE)

Parameter	Placebo (N=153)	Escitalopram (N=154)
HAMA	23.2 ± 0.3	23.6 ± 0.4
HAMA psychic anxiety subscale	13.3 ± 0.2	13.6 ± 0.2
CGI-S	4.2 ± 0.04	4.3 ± 0.04

3.1.6 Sponsor's Efficacy Results

The primary endpoint was the change from baseline to Week 8 in HAMA. Table 3.1.6.1 presents results of ANCOVA performed in ITT population using LOCF.

Table 3.1.6.1. ANCOVA for Change of HAMA (LOCF)

	Placebo (Mean ± SE)	Escitalopram (Mean ± SE)	P-value
SCT-MD-05	-7.7 ± 0.6	-9.6± 0.6	.044
SCT-MD-06	-7.6 ± 0.5	-9.2 ± 0.5	.032
SCT-MD-07	-7.4 ± 0.6	-11.3 ± 0.6	<.0001

Table 3.1.6.2 presents results of ANCOVA performed in ITT population using OC.

Table 3.1.6.2. ANCOVA for Change of HAMA (OC)

	Placebo (Mean ± SE)	Escitalopram (Mean ± SE)	P-value
SCT-MD-05	-8.6 ± 0.6	-10.5± 0.6	.176
SCT-MD-06	-8.0 ± 0.6	-9.8 ± 0.6	.007
SCT-MD-07	-8.2 ± 0.6	-12.9 ± 0.6	<.0001

3.1.7 Reviewer's Analysis

The reviewer validated the sponsor's analysis according to the protocol.

3.1.7.1 Analysis on Center

Since there was no procedure proposed in the protocol to pool centers with few patients, to assess whether small centers would affect the analysis, two models are compared: (I) ANCOVA with terms for treatment, center and baseline as covariate; and (II) ANCOVA with terms for treatment, and baseline as covariate.

Table 3.1.7.1.1 Comparison of Two Models

Study	I (w/ center)	II (w/o center)
SCT-MD-05	.0439	.0622
SCT-MD-06	.0319	.0342
SCT-MD-07	<.0001	<.0001

Table 3.1.7.1.2 presents number of positive (escitalopram is better than placebo) and negative centers. Detailed information on center is given in Section 3.1.7.2. There are large percentages of negative centers for SCT-MD-05 (36%), and SCT-MD-06 (37%).

Table 3.1.7.1.2 Number of Positive and Negative Centers

Study	Positive	Negative	Total
SCT-MD-05	16 (64%)	9 (36%)	25
SCT-MD-06	12 (63%)	7 (37%)	19
SCT-MD-07	19 (83%)	4 (17%)	23

Table 3.1.7.1.3 presents mean difference of E-P for center.

Table 3.1.7.1.3 Mean Difference of E-P for Center

Study	Mean (SD)
SCT-MD-05	-2.0 (5.1)
SCT-MD-06	-2.1 (4.3)
SCT-MD-07	-4.2 (4.3)

Checking Figures in Section 3.1.7.2, Center 01 in SCT-MD-05 has difference –11.5, and Center 05 in SCT-MD-06 has difference –14, respectively.

The differences relatively to mean differences are large which might be or might not be normal. If those centers are removed from the analysis, p-values for two models are presented in Table 3.1.7.1.4.

Table 3.1.7.1.4 Comparison of Two Models without Center 01 for SCT-MD-05 and Center 05 for SCT-MD-06

Study	I (w/ center)	II (w/o center)
SCT-MD-05	.0580	.0721
SCT-MD-06	.1534	.1511

Center 01 in SCT-MD-05 has 2 in placebo, and 1 in escitalopram groups, respectively. The means at baseline are 22.5 for placebo, and 27 for escitalopram, respectively. The following lists the detail information of all patients in Center 01. ANVIS is visit, VALUE is efficacy value, BSVALUE is baseline efficacy value, and CHANGE is change from baseline.

Obs	PID	TREATC	ANVIS	TESTDT	VALUE	BSVALUE	CHANGE
1	015114	Placebo	0	10/31/2000	19.00	19.00	.
2	015114	Placebo	1	11/08/2000	1.00	19.00	-18.00
3	015114	Placebo	2	11/16/2000	0.00	19.00	-19.00
4	015114	Placebo	4	11/28/2000	10.00	19.00	-9.00
5	015114	Placebo	6	.	10.00	19.00	-9.00
6	015114	Placebo	8	12/18/2000	10.00	19.00	-9.00
7	015115	Placebo	0	03/01/2001	26.00	26.00	.
8	015115	Placebo	1	03/06/2001	28.00	26.00	2.00
9	015115	Placebo	2	03/15/2001	17.00	26.00	-9.00
10	015115	Placebo	4	03/27/2001	16.00	26.00	-10.00
11	015115	Placebo	6	04/11/2001	15.00	26.00	-11.00
12	015115	Placebo	8	04/26/2001	16.00	26.00	-10.00
13	015113	Escitalopram	0	10/03/2000	27.00	27.00	.
14	015113	Escitalopram	1	10/10/2000	24.00	27.00	-3.00
15	015113	Escitalopram	2	10/18/2000	8.00	27.00	-19.00
16	015113	Escitalopram	4	10/31/2000	9.00	27.00	-18.00
17	015113	Escitalopram	6	11/14/2000	8.00	27.00	-19.00
18	015113	Escitalopram	8	11/28/2000	6.00	27.00	-21.00

Center 05 in SCT-MD-06 has 5 in placebo, and 6 in escitalopram groups, respectively. The means at baseline are 21.6 for placebo, and 23.33 for escitalopram, respectively. The following lists the detail information of all patients in Center 05.

Obs	PID	TREATC	ANVIS	TESTDT	VALUE	BSVALUE	CHANGE
1	056082	Placebo	0	06/27/2001	23	23	.
2	056082	Placebo	1	07/03/2001	25	23	2
3	056082	Placebo	2	07/11/2001	22	23	-1
4	056082	Placebo	4	07/24/2001	18	23	-5
5	056082	Placebo	6	.	18	23	-5
6	056082	Placebo	8	.	18	23	-5
7	056084	Placebo	0	07/13/2001	24	24	.
8	056084	Placebo	1	07/20/2001	13	24	-11
9	056084	Placebo	2	07/27/2001	12	24	-12
10	056084	Placebo	4	08/08/2001	17	24	-7
11	056084	Placebo	6	08/24/2001	21	24	-3
12	056084	Placebo	8	09/07/2001	22	24	-2
13	056085	Placebo	0	08/06/2001	19	19	.
14	056085	Placebo	1	08/13/2001	18	19	-1
15	056085	Placebo	2	08/17/2001	19	19	0
16	056085	Placebo	4	09/04/2001	12	19	-7
17	056085	Placebo	6	09/18/2001	13	19	-6
18	056085	Placebo	8	10/01/2001	14	19	-5
19	056086	Placebo	0	08/22/2001	22	22	.
20	056086	Placebo	1	08/29/2001	12	22	-10
21	056086	Placebo	2	09/05/2001	9	22	-13
22	056086	Placebo	4	09/14/2001	10	22	-12
23	056086	Placebo	6	10/03/2001	15	22	-7
24	056086	Placebo	8	10/17/2001	23	22	1
25	056291	Placebo	0	12/07/2001	20	20	.
26	056291	Placebo	1	12/13/2001	14	20	-6
27	056291	Placebo	2	12/20/2001	17	20	-3
28	056291	Placebo	4	01/03/2002	15	20	-5
29	056291	Placebo	6	01/17/2002	16	20	-4
30	056291	Placebo	8	02/04/2002	27	20	7
31	056081	Escitalopram	0	05/15/2001	27	27	.
32	056081	Escitalopram	1	05/22/2001	20	27	-7
33	056081	Escitalopram	2	05/29/2001	11	27	-16
34	056081	Escitalopram	4	06/12/2001	7	27	-20
35	056081	Escitalopram	6	06/26/2001	9	27	-18
36	056081	Escitalopram	8	07/10/2001	4	27	-23
37	056083	Escitalopram	0	06/29/2001	21	21	.
38	056083	Escitalopram	1	07/06/2001	17	21	-4
39	056083	Escitalopram	2	07/13/2001	15	21	-6
40	056083	Escitalopram	4	.	15	21	-6
41	056083	Escitalopram	6	.	15	21	-6
42	056083	Escitalopram	8	.	15	21	-6
43	056087	Escitalopram	0	08/27/2001	21	21	.
44	056087	Escitalopram	1	09/04/2001	14	21	-7
45	056087	Escitalopram	2	09/10/2001	8	21	-13
46	056087	Escitalopram	4	09/24/2001	13	21	-8
47	056087	Escitalopram	6	10/08/2001	4	21	-17
48	056087	Escitalopram	8	10/22/2001	12	21	-9
49	056088	Escitalopram	0	10/05/2001	23	23	.
50	056088	Escitalopram	1	.	23	23	0
51	056088	Escitalopram	2	10/16/2001	19	23	-4
52	056088	Escitalopram	4	11/02/2001	6	23	-17
53	056088	Escitalopram	6	11/16/2001	6	23	-17
54	056088	Escitalopram	8	11/30/2001	6	23	-17
55	056289	Escitalopram	0	10/17/2001	28	28	.
56	056289	Escitalopram	1	10/25/2001	17	28	-11
57	056289	Escitalopram	2	11/02/2001	12	28	-16
58	056289	Escitalopram	4	11/16/2001	16	28	-12
59	056289	Escitalopram	6	11/29/2001	9	28	-19
60	056289	Escitalopram	8	12/14/2001	6	28	-22
61	056290	Escitalopram	0	11/12/2001	20	20	.
62	056290	Escitalopram	1	11/20/2001	11	20	-9
63	056290	Escitalopram	2	11/26/2001	8	20	-12
64	056290	Escitalopram	4	12/10/2001	12	20	-8
65	056290	Escitalopram	6	12/27/2001	7	20	-13
66	056290	Escitalopram	8	01/10/2002	6	20	-14

Based on the large percentages of negative centers, and nonconsistent center effect size, the findings in SCT-MD-05 and SCT-MD-06 might not be robust.

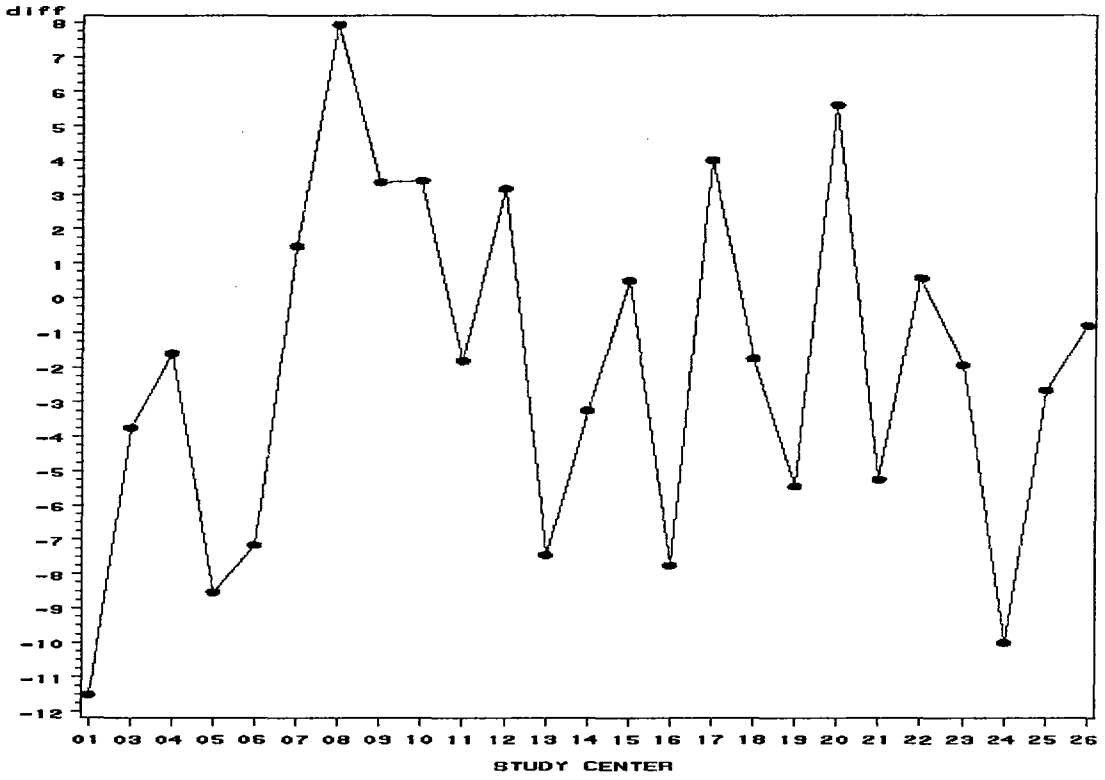
3.1.7.2 Information on Center

SCT-MD-05:

Table 3.1.7.2.1 Mean Difference of E – P by Center

Obs	CENTER	n_p	mean_p	n_t	mean_t	diff
1	01	2	-9.5000	1	-21.0000	-11.5000
2	03	4	-2.7500	4	-6.5000	-3.7500
3	04	5	-7.8000	5	-9.4000	-1.6000
4	05	3	-2.6667	5	-11.2000	-8.5333
5	06	6	-8.1667	9	-15.3333	-7.1667
6	07	4	-12.0000	2	-10.5000	1.5000
7	08	5	-15.6000	6	-7.6667	7.9333
8	09	8	-11.5000	7	-8.1429	3.3571
9	10	5	-11.6000	5	-8.2000	3.4000
10	11	10	-11.3000	9	-13.1111	-1.8111
11	12	6	-10.1667	5	-7.0000	3.1667
12	13	7	-2.4286	8	-9.8750	-7.4464
13	14	4	-5.7500	3	-9.0000	-3.2500
14	15	4	-8.5000	3	-8.0000	0.5000
15	16	8	-9.2500	7	-17.0000	-7.7500
16	17	2	-4.5000	2	-0.5000	4.0000
17	18	4	-6.2500	2	-8.0000	-1.7500
18	19	4	-7.7500	5	-13.2000	-5.4500
19	20	5	-8.4000	5	-2.8000	5.6000
20	21	4	-6.7500	4	-12.0000	-5.2500
21	22	7	-3.5714	5	-3.0000	0.5714
22	23	10	-5.7000	11	-7.6364	-1.9364
23	24	3	-0.6667	3	-10.6667	-10.0000
24	25	3	-2.3333	3	-5.0000	-2.6667
25	26	5	-7.8000	5	-8.6000	-0.8000

Figure 3.1.7.2.1 Mean Difference of E – P by Center



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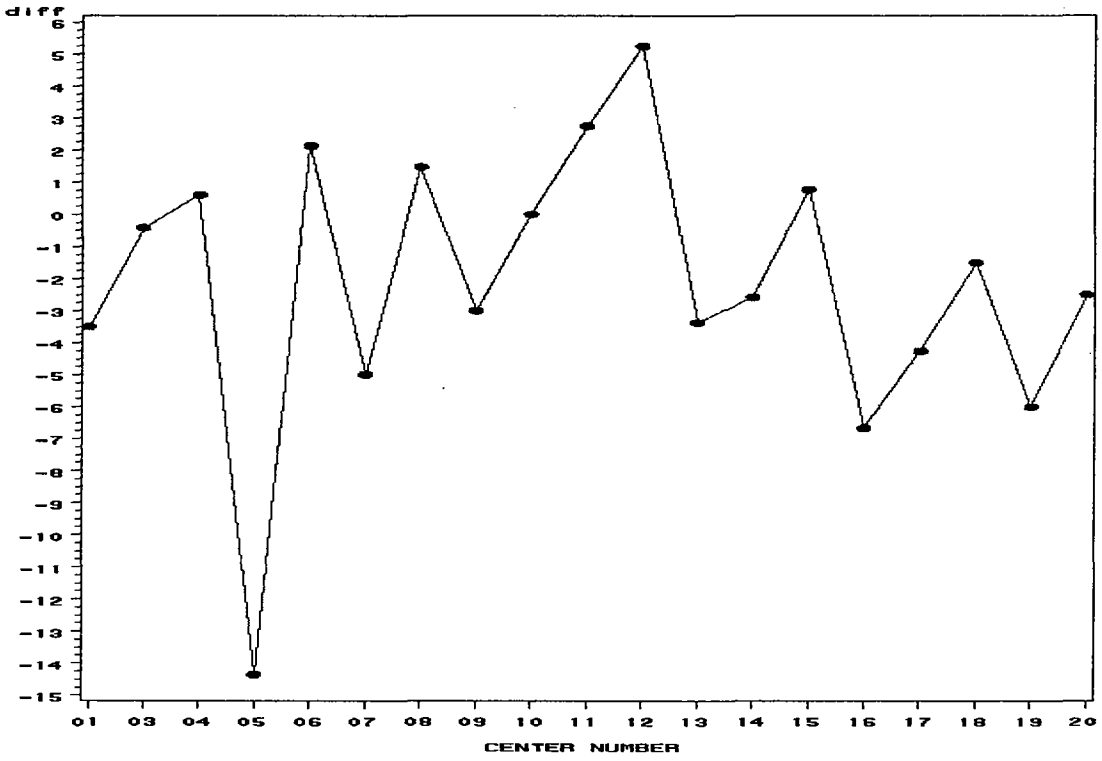
SCT-MD-06:

Table 3.1.7.2.2 Mean Difference of E – P by Center

Obs	CENTER	n_p	mean_p	n_t	mean_t	diff
1	01	5	-3.0000	6	-6.5000	-3.5000
2	03	12	-5.8333	12	-6.2500	-0.4167
3	04	5	-6.6000	5	-6.0000	0.6000
4	05	5	-0.8000	6	-15.1667	-14.3667
5	06	7	-9.4286	10	-7.3000	2.1286
6	07	7	-10.0000	8	-15.0000	-5.0000
7	08	6	-6.6667	5	-5.2000	1.4667
8	09	2	-5.0000	4	-8.0000	-3.0000
9	10	10	-11.4000	10	-11.4000	0.0000
10	11	2	-9.0000	4	-6.2500	2.7500
11	12	12	-12.5833	12	-7.3333	5.2500
12	13	10	-2.3000	9	-5.6667	-3.3667
13	14	10	-12.6000	11	-15.1818	-2.5818
14	15	12	-9.6667	10	-8.9000	0.7667
15	16	3	-5.6667	3	-12.3333	-6.6667
16	17	10	-5.3000	9	-9.5556	-4.2556
17	18	12	-6.5833	12	-8.0833	-1.5000
18	19	4	-6.0000	3	-12.0000	-6.0000
19	20	4	-6.2500	4	-8.7500	-2.5000

Figure 3.1.7.2.2 Mean Difference of E – P by Center



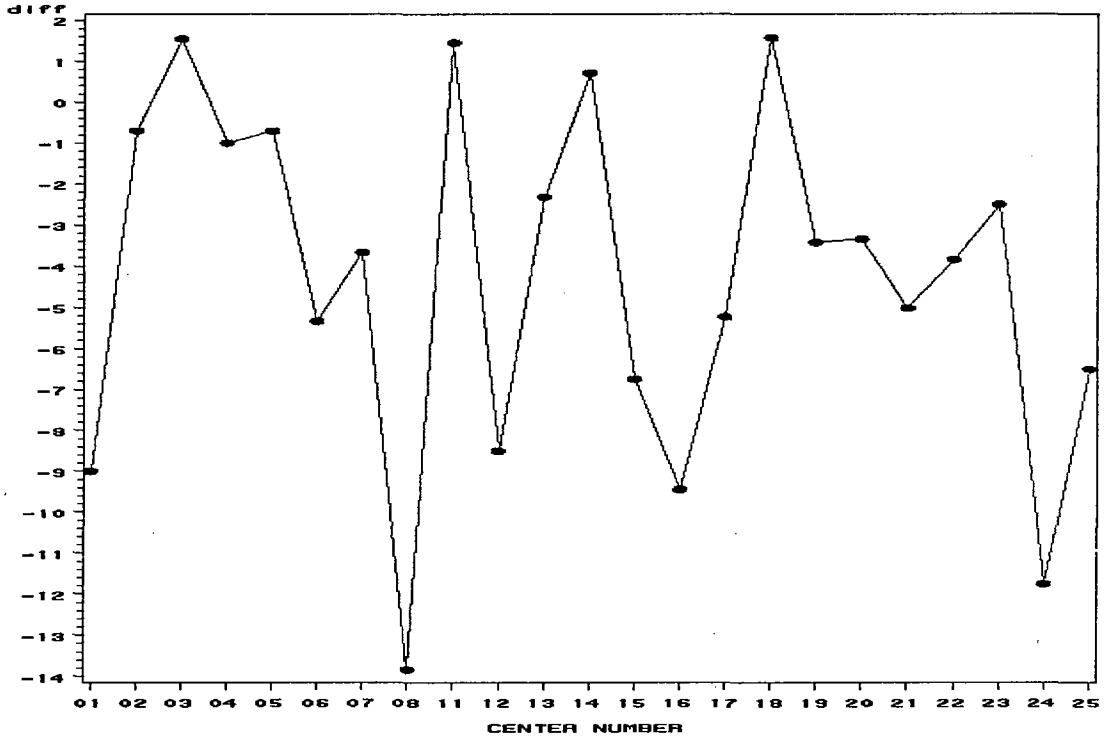
SCT-MD-07:

Table 3.1.7.2.3 Mean Difference of E – P by Center

Obs	CENTER	n_p	mean_p	n_t	mean_t	diff
1	01	2	-2.0000	3	-11.0000	-9.0000
2	02	10	-7.8000	10	-8.5000	-0.7000
3	03	4	-15.7500	5	-14.2000	1.5500
4	04	5	-6.0000	4	-7.0000	-1.0000
5	05	10	-4.3000	9	-5.0000	-0.7000
6	06	9	-4.7778	9	-10.1111	-5.3333
7	07	5	-9.0000	6	-12.6667	-3.6667
8	08	6	-2.0000	6	-15.8333	-13.8333
9	11	8	-10.6250	6	-9.1667	1.4583
10	12	4	-1.7500	4	-10.2500	-8.5000
11	13	12	-12.0833	10	-14.4000	-2.3167
12	14	7	-13.7143	9	-13.0000	0.7143
13	15	4	-7.5000	4	-14.2500	-6.7500
14	16	9	-2.2222	9	-11.6667	-9.4444
15	17	9	-6.1111	6	-11.3333	-5.2222
16	18	8	-9.3750	10	-7.8000	1.5750
17	19	6	-9.3333	4	-12.7500	-3.4167
18	20	9	-12.2222	10	-15.5615	-3.3393
19	21	11	-3.8182	12	-8.8333	-5.0152
20	22	5	-5.0000	6	-8.8333	-3.8333
21	23	4	-17.0000	6	-19.5000	-2.5000

22	24	4	-1.0000	4	-12.7500	-11.7500
23	25	2	-1.5000	2	-8.0000	-6.5000

Figure 3.1.7.2.3 Mean Difference of E – P by Center



3.2 Evaluation of Safety

See Clinical Review by Dr. Karen Brugge.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Table 4.1.1 indicates that escitalopram has greater change from baseline to week 8 of HAMA than placebo for both male and female for each study.

Table 4.1.1 Mean Change of HAMA by Gender

Study	Gender	Placebo		Escitalopram		E - P
		N	Mean	N	Mean	
SCT-MD-05	Male	48	-7.9	50	-8.1	-0.2

	Female	80	-7.6	74	-10.6	-3.0
SCT-MD-06	Male	70	-8.0	56	-9.2	-1.2
	Female	68	-7.3	87	-9.2	-1.9
SCT-MD-07	Male	71	-7.3	73	-11.1	-3.7
	Female	82	-7.6	81	-11.5	-3.9

Since majority subjects are white, no separate analysis on race is performed.

Table 4.1.21 indicates that escitalopram has greater change from baseline to week 8 of HAMA than placebo for two age groups except SCT-MD-06 ≥ 65 for each study.

Table 4.1.2 Mean Change of HAMA by Age

Study	Age	Placebo		Escitalopram		E - P
		N	Mean	N	Mean	
SCT-MD-05	< 65	121	-7.7	118	-9.4	-1.7
	≥ 65	7	-8	6	-13.3	-5.3
SCT-MD-06	< 65	133	-7.7	142	-9.2	-1.5
	≥ 65	5	-5.4	1	-1	4.4
SCT-MD-07	< 65	146	-7.6	148	-11.5	-3.9
	≥ 65	7	-4.9	6	-7.3	-2.4

4.2 Other Special/Subgroup Populations

There is no analysis performed for other subgroup.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Three studies showed that escitalopram group had greater mean change from baseline to Week 8 in HAMA than placebo group. The analyses are nominally statistically significant.

However, there are large percentages of negative centers in SCT-MD-05 (36%) and SCT-MD-06 (37%), and the results are very sensitive to its center. One should interpret the results with caution since the findings might not be robust.

5.2 Conclusions and Recommendations

The data and analysis from the current submission support the sponsor's claim but one should

interpret the result with caution since the findings might not be robust.

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Kun He
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Kun Jin
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BIOMETRICS

George Chi
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BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-003 & 21-365/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-323/SE1-003 & 21-365/SE1-004

Trade Name Lexapro Tablets (NDA 21-323)& Solution (NDA 21-365)
Generic Name escitalopram oxalate
Applicant Name Forest Pharmaceuticals
HFD-120
Approval Date December 18, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /___/

   b) Is it an effectiveness supplement? YES /__X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-323

NDA # 21-365

NDA #

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # SCT-MD-05

Investigation #2, Study # SCT-MD-06

Investigation #3, Study # SCT-MD-07

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /__X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # SCT-MD-05

Investigation #__, Study # SCT-MD-06

Investigation #__, Study # SCT-MD-07

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the

conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 58,380 YES /__X_/ NO /___/ Explain:

Investigation #2

IND # 58,380 YES /_X__/ NO /___/ Explain:

Investigation #2

IND # 58,380 YES /_X__/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2		
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

Richardae Taylor, Pharm.D.

Signature of Preparer Date
Title: Regulatory Project Manager

Russell Katz, M.D.

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Russell Katz
1/8/04 02:48:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-822/S-023
NDA 21-046/S-005
NDA 21-323/S-003/S-007/S-010
NDA 21-365/S-001/S-004/S-005

Forest Laboratories, Inc.
Attention: Andrew Friedman, R.Ph.
Manager, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Dear Mr. Friedman:

Please refer to your supplemental new drug applications dated June 6, received June 9, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celexa (citalopram hydrobromide) 10 mg, 20 mg and 40 mg Tablets (20-822/S-023), Celexa (citalopram hydrobromide) 10 mg/5 ml Oral Solution (21-046/S-005), Lexapro (escitalopram oxalate) 5 mg, 10 mg[ ] Tablets (21-323/S-010), and Lexapro (escitalopram oxalate) 5 mg/5 ml Oral Solution (21-365/S-005).

We acknowledge receipt of your submissions dated January 9, 2004, to supplemental applications 20-822/S-023 and 21-046/S-005.

These submissions constituted a complete response to our December 9, 2003 action letter.

We additionally acknowledge receipt of your submission dated January 20, 2004, providing for 20 copies of FPL as requested in our December 18, 2003, approval letter for supplemental applications 21-323/S-003/S-007 and 21-365/S-001/S-004.

Supplemental applications 20-822/S-023 and 21-046/S-005, submitted as "Changes Being Effected" supplements, provide for changes to the **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections to incorporate selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) class labeling changes in regards to bleeding related adverse events, discontinuation symptoms, and to adverse events occurring in neonates exposed to any of the SSRIs or SNRIs late in the third trimester.

We have completed the review of your resubmissions, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your January 9, 2004 labeling. Accordingly, these applications are approved effective on the date of this letter.

We have also reviewed your final printed labeling submitted on January 20, 2004, and it is acceptable. Therefore, this labeling will be retained in our files.

Additionally, since our approval letter dated December 18, 2003, supercedes the labeling revisions proposed in supplemental applications 21-323/S-010 and 21-365/S-005, we are going to administratively close these supplements and retain them in our files.

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, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
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REGULATORY PROJECT MANAGER
LABELING REVIEW

Celexa (citalopram Hydrobromide) Tablets (NDA 20-822)
Celexa (citalopram Hydrobromide) Oral Solution (NDA 21-046)
Lexapro (escitalopram Hydrobromide) Tablets (NDA 21-323)
Lexapro (escitalopram Hydrobromide) Solution (NDA 21-365)

Date:	March 20, 2004	
DRUG:	**Celexa Tablets (NDA 20-822)**	**Celexa Solution (NDA 21-046)**
Supplements:		
(last approved)	SLR-019 (AP date 11-19-02)	SLR-003 (AP date 11-19-02)
(pending action)	SLR-023 (dated 6-6-03)	SLR-005 (dated 6-6-03)
DRUG:	**Lexapro Tablets (NDA 21-323)**	**Lexapro Solution (NDA 21-365)**
Supplements:		
(last approved)	SE1-003/SE8-007 (AP 12-18-03)	SE1-004/SE8-001 (AP 12-18-03)
(pending action)	SLR-010 (dated 6-6-03)	SLR-005 (dated 6-6-03)

- Approvable letter for 20-822/SLR-023, 21-046/SLR-005, 21-323/SLR-010, and 21-365/SLR-005 issued on 12-9-03. Forest responded to the 12-9-03 AE letter only to labeling supplements 20-822/SLR-023 & 21-046/SLR-005 in a resubmission dated 1-9-04.
- Forest submitted FPL for efficacy supplements 21-323/SE1-003/SE8-007 & 21-365/SE1-004/SE8-001 in a submission dated 1-20-04 as requested in the Agency approval letter for these efficacy supplements dated 12-18-03.

Notes of interest:

- The Agency issued an AE letter for NDAs 20-822/SLR-023, 21-046/SLR-005, 21-323/SLR-010, & 21-365/SLR -005 in an action dated 12-9-03. These supplements provided for class labeling bleeding related adverse event (BRAE) changes to labeling. Subsequent to the 12-9-03 action letter, the Agency was able to incorporate the BRAE labeling changes into the approval letter dated 12-18-03, for Lexapro in generalized anxiety disorder and additional MDD studies (NDAs 21-323/SE1-003/SE8-007 & 21-365/SE1-004/SE8-001). The 12-18-03 AP action letter also incorporated the class labeling for all of the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), to change labeling in regards to discontinuation symptoms and to adverse events occurring in neonates exposed to any of the SSRIs or SNRIs late in the third trimester. At the time of labeling negotiation for the Lexapro efficacy supplements, Forest agreed to make the class labeling revisions to the Celexa labeling.

REVIEW

20-822/SLR-023
21-046/SLR-005
RS Dated: 1-9-04
CBE: Yes

Reviewed by Medical Officer: Not necessary (see conclusions)

- These supplements provide for revisions to the WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections to incorporate the class labeling BRAE, discontinuation, and adverse events occurring in neonates exposed to any of the SSRIs or SNRIs late in the third trimester to product labeling.

CONCLUSIONS

1. These supplements only provide for the labeling revisions as listed above when compared to the last approved FPL.
2. Forest did not submit a response to the Lexapro labeling supplements, NDAs 21-323/SLR-010 & 21-365/SLR-005, since the approval of the efficacy supplements incorporated the requested changes.
3. The FPL submitted in response to the Lexapro efficacy supplement approval letter dated 12-19-03 is identical to the labeling attached to the approval letter.
4. I recommend that a) Celexa labeling supplements 20-822/SLR-023 and 21-046/SLR-005 be approved, b) Lexapro labeling supplements 21-323/SLR-010 and 21-365/SLR-005 be retained since this labeling was superceded by the approval of the Lexapro efficacy labeling supplements, and c) an acknowledge and retain action issue for the FPL that was submitted in response to the approval of the Lexapro labeling supplements, 21-323/SE1-003/SE8-007 and 21-365/SE1-004/SE8-001.
5. I also recommend that this review, alone, be sufficient to close these supplements since they were purely administrative in nature.

Paul David. RPh
Senior Regulatory Project Manager

Robbin Nighswander, R.Ph
Supervisory Regulatory Health Officer

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/s/

Paul David
3/30/04 10:16:18 AM
CSO

Robbin Nighswander
3/30/04 12:52:54 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 21-323/S-003 & 21-365/S-004

Forest Laboratories, Inc.
Attention: Andrew Friedman, RPh
Manager, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Mr. Friedman:

We acknowledge receipt on October 21, 2003 of your October 20, 2003 resubmission to your supplemental new drug applications for Lexapro ™ (escitalopram oxalate) Tablets (NDA 21-323/S-003) and Oral solution (NDA 21-365/S-004).

We consider this a complete, class 1 response to our September 26, 2003 action letter. Therefore, the primary user fee goal date is December 21, 2003 and the secondary user fee goal date is April 21, 2004.

If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Supervisory Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robbin Nighswander
10/27/03 03:22:13 PM

FOREST LABORATORIES, INC.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Direct Line: (201) 386-2117
Fax: (201) 524-9711

ORIGINAL

October 20, 2003

Russell G. Katz, MD, Director
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Attn: Document Room HFD-120
1451 Rockville Pike
Rockville, MD 20852

SEI-003 (BZ) A2
SEI 004 (BZ) A2

NDA: **21-323/ S-003 Lexapro™ (Escitalopram Oxalate) Tablets**
NDA: 21-365/S-004 Lexapro™ (Escitalopram Oxalate) Oral Solution
Re: **Response to FDA Approvable Letter: Generalized Anxiety Disorder (GAD)**

Dear Dr. Katz:

Reference is made to the September 26, 2003 approvable letter for the subject supplemental NDA. Forest Laboratories, Inc. submits herewith, in duplicate, a response to each of the items addressed in the letter.

Chemistry Issues

- As discussed in a telephone conversation with Ms. Anna Marie H. Weikel on October 2, 2003, Forest Labs notes that the chemistry issues identified in the approvable letter for the GAD sNDA do not apply to the studies submitted with this application to support the proposed indication. The efficacy trials, SCT-MD-05, SCT-MD-06, and SCT-MD-07, were double-blind placebo controlled studies comparing the safety and efficacy of escitalopram and matching placebo tablets. Encapsulation was not used in any of these studies nor was citalopram.

Labeling

- The attached package insert has been revised as requested (**Attachment 1**). Additional proposed labeling modifications are indicated by strike outs (~~removed text~~) and underlined highlighted text (new text). We have used as our base labeling the currently approved package insert now in production (version 12/02) which includes the oral solution labeling. To facilitate review, labeling is also provided electronically as a Microsoft WORD® file on the enclosed diskette. The diskette has been scanned and is free from computer viruses.

Safety Update

- A final safety update including serious events up to September 1, 2003 is attached (**Attachment 2**).

Regulatory Status Update

Attached is information regarding the worldwide regulatory status of escitalopram as of October 2, 2003 **(Attachment 3)**.

Worldwide Literature Update

Attached is an updated worldwide literature search for escitalopram with a cutoff date of September 30, 2003 **(Attachment 4)**.

If you have any questions related to this submission, please call me at (201) 386-2117 or in my absence, Michael Macalush at (201) 386-2007.

Sincerely,

Andrew Friedman, RPh
Manager, Regulatory Affairs
Andrew.Friedman@frx.com

Desk Copies w/ Att (8): Mr. Robbin Nighswander, RPh., Chief, Project Management Staff, HFD-120

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: September 4, 2003

TO: Anna Marie Homonnay-Weikel, Regulatory Health Project Manager
Karen Brugge, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-323/SE1-003

APPLICANT: Forest Laboratories, Inc.

DRUG: Escitalopram oxalate (Lexapro) Tablets

THERAPEUTIC CLASSIFICATION: Type S

INDICATION: Generalized Anxiety Disorder (GAD)

CONSULTATION REQUEST DATE: January 13, 2003

ACTION GOAL DATE: September 27, 2003

I. BACKGROUND:

Escitalopram oxalate (Lexapro™) is the S-entiomer of the selective serotonin reuptake inhibitor citalopram, both of which are approved for treatment of depression. In this application, the sponsor has requested for the treatment of generalized anxiety disorder (GAD). The application is based on protocols SCT-MD-05, SCT-MD-06 and SCT-MD-07 ("Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder").

Each study consists of a one-week single blind placebo lead-in period, followed by an eight-week double-blind treatment (escitalopram vs. placebo) period. Subjects must meet the DSM-IV

diagnosis of GAD. Subject must have a score of 18 or higher on the Hamilton Anxiety scale (HAM-A) with a minimum score of 2 on the tension and anxiety items at screening and baseline. The primary endpoint was change from baseline on the HAM-A at week 8.

Inspection assignment was issued in February 2003 for two domestic sites: Drs. David and Holland because these investigators enrolled a large number of subjects in the protocol. This data audit assignment also included the review division request for two additional sites in June 2003: Drs. Amsterdam and Burke as the Statistical Reviewer identified these sites as outliers during the review process.

II. RESULTS (by site):

NAME	Protocol	Location	ASSIGNED DATE	EIR RECEIVED DATE	CLASSIFICATION
Dr. J. David	SCT-MD-05 and 07	Charlottesville, VA	02-20-2003	07-01-2003	VAI
Dr. P. Holland	SCT-MD-05 and 06	Boca Raton, FL	02-20-2003	05-12-2003	NAI
Dr. W. Burke	SCT-MD-06	Omaha, NE	06-26-2003	08-04-2003	NAI
Dr. J. Amsterdam	SCT-MD-05	Philadelphia, PA	06-26-2003	pending	pending*

*Final classification pending; based on electronic mail and telecommunication with the FDA field investigator.

DAVID, M.D.

At this site, two identical protocols (protocols SCT-MD-05 and SCT-MD-07 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder") were used.

For Protocol SCT-MD-05, 15 subjects were enrolled and randomized; 10 subjects completed the study. Five subjects discontinued from the study. The reason for discontinuation was listed as withdrawal of consent (2 subjects from placebo group) and lost to follow up (2 subjects from placebo and 1 subject from escitalopram). An audit of 10 subjects' records was conducted.

For Protocol SCT-MD-07, 18 subjects were enrolled and randomized; 16 subjects completed the study. Two subjects from escitalopram group discontinued from the study. The reasons for discontinuation were listed as protocol violation and adverse event. An audit of 10 subjects' records was conducted.

A two-item Form FDA 483 was issued at the end of inspection. Inspectional findings included: Subject 7160 and 7262 enrolled in SCT-MD-07 had abnormal thyroid stimulating hormone (TSH) levels of 5.12 uIU/ml and 10.51 uIU/ml respectively (normal range 0.49-4.67). Dr. David

reviewed these values as clinically significant. Dr. David stated that the condition was pre-existing and stable for both subjects. However, he did not obtain the documented approval of the Medical Monitor for enrollment of these subjects as specified in the protocol. The adverse events of erectile dysfunction and delayed orgasm experienced by subject 7007 were not reported to the sponsor.

All subjects signed the informed consent. Overall, data appear acceptable.

HOLLAND, M.D.

At this site, two identical protocols (protocols SCT-MD-05 and SCT-MD-06 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder") were used.

For Protocol SCT-MD-05, 27 subjects were screened; 15 subjects were randomized and 12 subjects completed the study. Three subjects discontinued from the study. Their reason for discontinuation was listed as withdrawal of consent. An audit of 15 subjects' records was conducted. No Form FDA 483 was issued. Minor drug accountability issue was noted in that there was one dose difference for four subjects (5224, 5222, 5179 and 5187) during one of the study visits. However, it was documented that subjects took prescribed dose of medication and any missing dose was reported to the sponsor.

For Protocol SCT-MD-06, 28 subjects were screened; 12 subjects were randomized and 9 subjects completed the study. Three subjects discontinued from the study. The reasons for discontinuation included nausea, work obligation and lost to follow up. An audit of 12 subjects' records was conducted. No Form FDA 483 was issued. Minor drug accountability was noted that there was one dose difference for two subjects (6099 and 6095) during one of the study visits. However, it was documented that subjects took prescribed dose of medication and any missing dose was reported to the sponsor.

All subjects participated in both studies signed the informed consent. Overall, data appear acceptable.

BURKE, M.D.

At this site, protocol SCT-MD-06 was used. 14 subjects were screened; 11 subjects were randomized; and 9 subjects completed the study.

An audit of all randomized subjects' records was conducted. No Form FDA 483 was issued. All primary efficacy variables provided in data listing were compared to the CRF and no deviations were found. There was no issue on test article accountability records. No underreporting of adverse events was noted at this site. All subjects signed the informed consent. Overall, data appear acceptable.

AMSTERDAM, M.D.

At this site, only 3 subjects were enrolled. Based on communication with the FDA field investigator, it was revealed that all 3 subjects (#5113, 5114 and 5115) met the inclusion/exclusion criteria. There was no discrepancy in primary efficacy measure (HAM-A scores) which were collected at all study visits from baseline to the end of study, between the source document, CRF and data listing provided by the sponsor. All subjects signed the consent form. No Form FDA 483 was issued. Data seem acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol and amendments. Except for instances of regulatory violations at Dr. David's site as stated above, data from these centers that had been inspected appear acceptable for use in support of this supplemental NDA.

[Note: The review and evaluation of Dr. Amsterdam's audit was based on preliminary input from the field investigator via electronic mail and telecommunication. Should the EIR and exhibits from the audit, when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly.]

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

cc:
NDA 21-323/SE1-003
HFD-45/Division File / Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U
HFD-46/Khin
HFD-46/Friend
HFD-46/George GCPB1 Files

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/s/

Ni Aye Khin
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MEDICAL OFFICER

Khin U
9/4/03 02:53:25 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Jay Amsterdam, M.D.
Depression Research Unit
University of Pennsylvania
3535 Market Street
Philadelphia, Pennsylvania 19104

SEP 25 2003

Dear Dr. Amsterdam:

On September 2 and 3, 2003, Mr. Mike M. Rashti, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol SCT-MD-05 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder") of the investigational drug escitalopram (Lexapro), performed for Forest Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Rashti during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003068423
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA#21-323/SE1-003
HFD-120 Review Div.Dir. Katz
HFD-120 MO Brugge
HFD-120 PM Homonnay-Weikel
HFD-46 c/r/s/ GCP File #10162
HFD-46 MO Khin
HFD-46 CSO Friend
HFR-CE150 DIB Baker
HFR-CE1515 Bimo Tamariello
HFR-CE150 Field Investigator Rashti
GCF-1 Seth Ray

r/d: (NK): 9/17/03
reviewed:KMU:9/17/03
f/t:sg:9/22/03

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Reviewer Note to Rev. Div. M.O.

- This data audit inspection was conducted per the review division request as the statistical reviewer identified this site as an outlier during the review.
- At this site, protocol SCT-MD-05 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder" was used.
- 4 subjects were screened; 3 subjects were randomized; and all 3 subjects completed the study. An audit of all randomized subjects' records was conducted.
- No Form FDA 483 was issued.
- In the EIR, it was noted that all primary efficacy variables provided in data listing were compared to the CRF and no deviations were found.
- There was no issue on test article accountability records.
- No underreporting of adverse events was noted at this site.
- All subjects signed the informed consent.
- Overall, data appear acceptable.

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/s/

Khin U
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG - 7 2003

William J. Burke, M.D.
University of Nebraska Medical Center
Department of Psychiatry
985581 Nebraska Medical Center
Omaha, Nebraska 68198-5581

Dear Dr. Burke:

Between July 22 and 24, 2003, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol SCT-MD-06 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder") of the investigational drug escitalopram (Lexapro), performed for Forest Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3001451216
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA#21-323/SE1-003
HFD-120 Review Div.Dir. Katz
HFD-120 MO Brugge
HFD-120 PM Homonnay-Weikel
HFD-46 c/r/s/ GCP File #9411
HFD-46 MO Khin
HFD-46 CSO Friend
HFR-SW350 DIB Thorsky
HFR-SW350 Bimo Monitor & Field Investigator Montgomery
GCF-1 Seth Ray

r/d: (NK): 8/5/03
reviewed:UK: 8/03
f/t:sg:8/7/03

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Reviewer Note to Rev. Div. M.O.

- At this site, protocol SCT-MD-06 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder" was used.
- 14 subjects were screened; 11 subjects were randomized; and 9 subjects completed the study. An audit of all randomized subjects' records was conducted.
- No Form FDA 483 was issued.
- In the EIR, it was noted that all primary efficacy variables provided in data listing were compared to the CRF and no deviations were found.
- There was no issue on test article accountability records.
- No underreporting of adverse events was noted at this site.
- All subjects signed the informed consent.
- Overall, data appear acceptable.

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/s/

Khin U
8/14/03 03:27:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Joseph David, M.D.
535 Westfield Road, Suite 102
Charlottesville, Virginia 2211

JUL 17 2003

Dear Dr. David:

Between June 9 and 12, 2003, Ms. Candice C. Mandera, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of two clinical investigations (protocols SCT-MD-05 and SCT-MD-07 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder") of the investigational drug escitalopram (Lexapro), performed for Forest Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Mandera presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

Protocol SCT-MD-07

1. You did not adhere to the investigational plan [21 CFR 312.60]. You enrolled two subjects (7160 and 7262) who had elevated thyroid stimulating hormone levels that were clinically significant and without obtaining documented approval from the Medical Monitor for their enrollment.

2. You did not report to the sponsor the adverse events of erectile dysfunction and delayed orgasm experienced by subject 7007 [21 CFR 312.64(b)].

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

Page 2- Joseph David, M.D.

We appreciate the cooperation shown Investigator Mandera during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3- Joseph David, M.D.

FEI: 3003936463
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X _2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:
__X__failure to adhere to protocol (05)
__X__failure to report ADRS (16)
Deficiency Codes: 5, 16

cc:
HFA-224
HFD-120 Doc.Rm. NDA#21-323/SE1-003
HFD-120 Review Div.Dir. Katz
HFD-120 MO Brugge
HFD-120 PM Homonnay-Weikel
HFD-47c/r/s/ GCP File #10943
HFD-46 MO Khin
HFD-46 CSO Friend
HFR-CE250 DIB Wagner
HFR-CE250 Bimo Monitor Salisbury
HFR-CE2545 Field Investigator Mandera
GCF-1 Seth Ray

r/d: (NK): 07/15/03
reviewed: UK:07/16/03
f/t:sg/: 07/16/03
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Page 4- Joseph David, M.D.

Reviewer Note to Rev. Div. M.O.

- At this site, two identical protocols (protocols SCT-MD-05 and SCT-MD-07 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder") were used.

  Protocol SCT-MD-05: 15 subjects were enrolled and randomized; 10 subjects completed the study. Five subjects discontinued from the study. The reason for discontinuation was listed as withdrawal of consent (2 subjects from placebo group) and lost to follow up (2 subjects from placebo and 1 subject from escitalopram). An audit of 10 subjects' records was conducted.

  Protocol SCT-MD-07: 18 subjects were enrolled and randomized; 16 subjects completed the study. Two subjects from escitalopram group discontinued from the study. The reasons for discontinuation were listed as protocol violation and adverse event. An audit of 10 subjects' records was conducted.

- A two-item Form FDA 483 was issued at the end of inspection.
  Inspectional findings:
  1) Subject 7160 and 7262 enrolled in SCT-MD-07 had abnormal thyroid stimulating hormone (TSH) levels of 5.12 uIU/ml and 10.51 uIU/ml respectively (normal range 0.49-4.67). Dr. David reviewed these values as clinically significant. During the closeout, Dr. David stated that the condition was pre-existing and stable for both subjects. However, he did not obtain the documented approval of the Medical Monitor for enrollment of these subjects as specified in the protocol.
  2) The adverse events of erectile dysfunction and delayed orgasm experienced by subject 7007 were not reported to the sponsor.

- All subjects signed the informed consent.

- Overall, data appear acceptable.

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/s/

Khin U
7/21/03 09:18:56 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 21 2003

Peter Holland, M.D.
Summit Research Network
Florida/Boca Raton Medical Research Inc.
7284 West Palmetto Park Road
Suite 205, South Plaza
Boca Raton, Florida 33433

Dear Dr. Holland:

Between April 16 and 23, 2003, Mr. Sean T. Creighton, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of two clinical investigations (protocols SCT-MD-05 and SCT-MD-06 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder") of the investigational drug escitalopram (Lexapro), performed for Forest Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Creighton during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Antoine El-Hage

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003936486
Field Classification: In compliance; Refer to HFD-47
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA#21-323/SE1-003
HFD-120 Review Div.Dir. Katz
HFD-120 MO Brugge
HFD-120 PM Homonnay-Weikel
HFD-47c/r/s/ GCP File #10897
HFD-47 MO Khin
HFD-47 CSO Friend
HFR-SE250 DIB Gallant
HFR-SE250 Bimo Monitor Torres
HFR-SW2590 Field Investigator Creighton
GCF-1 Seth Ray

r/d: (NK): 5/13/03
reviewed:AEH: 5/15/03
f/t:ml/: 5/15/03
O:\NK_Letters\Holland.nai.doc

Reviewer Note to Rev. Div. M.O.

- At this site, two identical protocols (protocols SCT-MD-05 and SCT-MD-06 entitled "Flexible Dose Comparison of the Safety and Efficacy of Escitalopram and Placebo in the Treatment of Generalized Anxiety Disorder") were used.
- Protocol SCT-MD-05: 27 subjects were screened; 15 subjects were randomized and 12 subjects completed the study. Three subjects discontinued from the study. Their reason for discontinuation was listed as withdrawal of consent.
  An audit of 15 subjects' records was conducted. No Form FDA 483 was issued. Minor drug accountability issue was noted in that there was one dose difference for four subjects (5224, 5222, 5179 and 5187) during one of the study visits. However, it was documented that subjects took prescribed dose of medication and any missing dose was reported to the sponsor.
- Protocol SCT-MD-06: 28 subjects were screened; 12 subjects were randomized and 9 subjects completed the study. Three subjects discontinued from the study. The reasons for discontinuation included nausea, work obligation and lost to follow up.
  An audit of 12 subjects' records was conducted. No Form FDA 483 was issued. Minor drug accountability was noted that there was one dose difference for two subjects (6099 and 6095) during one of the study visits. However, it was documented that subjects took prescribed dose of medication and any missing dose was reported to the sponsor.
- All subjects signed the informed consent.
- Overall, data appear acceptable.

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/s/

Antoine El-Hage
5/23/03 11:32:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING ISSUES IDENTIFIED

NDA 21-365/S-004

Forest Laboratories, Inc.
Attention: Andrew Friedman, R.Ph.
Manager, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Mr. Friedman:

Please refer to your May 21, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) oral solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on July 22, 2003 in accordance with 21 CFR 314.101(a).

We note that this supplemental application relies upon your companion supplemental application for Lexapro (escitalopram oxalate) tablets (S-003) dated November 26, 2002.

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}

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

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/s/

Thomas Laughren
7/31/03 04:06:36 PM
Signed for Russell Katz, M.D.

MEMORANDUM

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

DATE: June 10, 2003

TO: NDA 21-365/S-004 Administrative File

FROM: Anna Marie H. Weikel
Senior Regulatory Health Project Manager

SUBJECT: 45-day Filing Issues
NDA 21-365/S-004, Lexapro (escitalopram oxalate) oral solution

Reference is made to NDA 21-323/S-003 submitted on 11/26/03 for an efficacy supplement for Generalized Anxiety Disorder for LEXAPRO Tablets. The firm, Forest Laboratories, inadvertently did not cross reference the oral solution in that filing. The purpose of this supplement is to add the oral solution to this efficacy supplement. There is absolutely no data in this supplement except for what is cross referenced to NDA 21-323/S-003 which was filed by the Agency already. Therefore there are no filing issues identified with this supplement.

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/s/

Anna-Marie Homonnay
6/10/03 10:16:26 AM
CSO

Anna-Marie Homonnay
6/10/03 10:18:13 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-365/S-004

Forest Laboratories, Inc.
Attention: Andrew Friedman, R.Ph.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Mr. Friedman:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lexapro™ (escitalopram oxalate) Oral Solution

NDA Number: 21-365

Supplement number: S-004

Date of supplement: May 21, 2003

Date of receipt: May 22, 2003

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 22, 2003, in accordance with 21 CFR 314.101(a).

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Senior Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Anna-Marie Homonnay
6/10/03 10:04:26 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-323/S-003

PRIOR APPROVAL SUPPLEMENT

Forest Laboratories, Inc.
Attention: Tracey Varner
Senior Manager, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Ms. Varner:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lexapro® (escitalopram oxalate) Tablets

Supplement Number: NDA 21-323/S-003

Review Priority Classification: Standard (S)

Date of Supplement: November 26, 2002

Date of Receipt: November 27, 2002

These supplements provide for the treatment of GeneralizedAnxiety Disorder as a new indication.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 27, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 27, 2003.

If you should have any questions, please call Anna Marie H. Weikel, R.Ph., Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Anna-Marie Homonnay
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