

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**21-323/S-007 & 21-365/S-001**

***Trade Name:*** Lexapro Tablets/Oral Solution

***Generic Name:*** escitalopram oxalate

***Sponsor:*** Forest Laboratories, Inc.

***Approval Date:*** December 18, 2003

***Indications:*** For the treatment of major depressive disorder

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RESEARCH**

*APPLICATION NUMBER:*

**21-323/S-007 & 21-365/S-001**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**21-323/S-007 & 21-365/S-001**

**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 escitalopram, 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

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/s/

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

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**21-323/S-007 & 21-365/S-001**

**APPROVABLE LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-323/S-007

NDA 21-365/S-001

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 February 6, received February 7, 2003, 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 amendments dated March 18, July 11, September 12, September 18, and October 13, 2003.

These supplements provide for the efficacy study reports from Studies 99001 & 99003 as additional trials supporting the efficacy of escitalopram in the treatment of major depressive disorder.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as stated below.

**Labeling**

Accompanying this letter (Enclosure) is the Agency's proposal for the labeling of escitalopram. Brackets [] embedded within the text that follows include comments and explanations concerning our proposed labeling. Therefore, we are requesting that Forest agree to the labeling attached to this action letter.

We are also taking this opportunity, in a class labeling initiative for all of the selective serotonin reuptake inhibitors (SSRIs), to change labeling in regards to discontinuation symptoms, abnormal bleeding, and adverse events occurring in neonates exposed to any of the SSRIs late in the third trimester.

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

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 this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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.

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

Enclosure

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

Approvable Letter

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/s/

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Russell Katz

11/25/03 07:20:46 AM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-323/S-007 & 21-365/S-001**

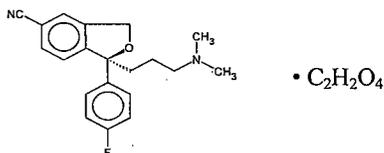
**LABELING**

**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-phthalanecarbonitrile oxalate with the following structural formula:



The molecular formula is C<sub>20</sub>H<sub>21</sub>FN<sub>2</sub>O • C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> 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-HT<sub>1-7</sub>) or other receptors including alpha- and beta-adrenergic, dopamine (D<sub>1-5</sub>), histamine (H<sub>1-3</sub>), muscarinic (M<sub>1-5</sub>), and benzodiazepine receptors. Escitalopram also does not bind to or has low affinity for various ion channels including Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup> and Ca<sup>++</sup> 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-HT<sub>1-7</sub>) or other receptors including alpha- and beta- adrenergic, dopamine (D<sub>1-5</sub>), histamine (H<sub>1-3</sub>), muscarinic (M<sub>1-5</sub>), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup> and Ca<sup>++</sup> 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<sub>max</sub> 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<sub>max</sub> and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

**Reduced hepatic function** - Escitalopram 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 escitalopram 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  $\leq 12$ . Relapse during the double-blind phase was defined as an increase of the MADRS total score to  $\geq 22$ , 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 C<sub>max</sub> 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 C<sub>max</sub> 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  $\geq 32$  mg/kg/day. Gestation duration was increased at 48 mg/kg/day.

### **Pregnancy**

#### Pregnancy Category C

In a rat embryo/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  $\geq 56$  times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [ $\text{mg}/\text{m}^2$ ] 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  $\text{mg}/\text{m}^2$  basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  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  $\geq 24$  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 \***

<u>Body System / Adverse Event</u>	<u>(Percentage of Patients Reporting Event)</u>	
	<u>LEXAPRO</u> (N=715)	<u>Placebo</u> (N=592)
<b>Autonomic Nervous System Disorders</b>		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
<b>Central &amp; Peripheral Nervous System Disorders</b>		
Dizziness	5%	3%
<b>Gastrointestinal Disorders</b>		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
<b>General</b>		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
<b>Psychiatric Disorders</b>		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
<b>Respiratory System Disorders</b>		
Rhinitis	5%	4%
Sinusitis	3%	2%
<b>Urogenital</b>		
Ejaculation Disorder <sup>1,2</sup>	9%	<1%
Impotence <sup>2</sup>	3%	<1%
Anorgasmia <sup>3</sup>	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  $\geq$  LEXAPRO: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety.

<sup>1</sup>Primarily ejaculatory delay.

<sup>2</sup>Denominator used was for males only (N=225 LEXAPRO ; N=188 placebo).

<sup>3</sup>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)
<b>Autonomic Nervous System Disorders</b>		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
<b>Central &amp; Peripheral Nervous System Disorders</b>		
Headache	24%	17%
Paresthesia	2%	1%
<b>Gastrointestinal Disorders</b>		
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%
<b>General</b>		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
<b>Musculoskeletal</b>		
Neck/Shoulder Pain	3%	1%
<b>Psychiatric Disorders</b>		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Yawning	2%	1%
<b>Urogenital</b>		
Ejaculation Disorder <sup>1,2</sup>	14%	2%
Anorgasmia <sup>3</sup>	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  $\geq$  LEXAPRO: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis.

<sup>1</sup>Primarily ejaculatory delay.

<sup>2</sup>Denominator used was for males only (N=182 LEXAPRO; N=195 placebo).

<sup>3</sup>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  $\geq$  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.

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

<b>TABLE 4</b>		
<b>Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials</b>		
<b>Adverse Event</b>	<b>LEXAPRO™</b>	<b>Placebo</b>
	<b>In Males Only</b>	
	(N= 407)	(N= 383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Decreased Libido	6%	2%
Impotence	2%	<1%
	<b>In Females Only</b>	
	(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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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-323/S-007 & 21-365/S-001**

**MEDICAL REVIEW**

CLINICAL REVIEW

NDA 21-323/SE8-007  
Cross-reference NDA 21-365/SE8-001

Sponsor: Forest Laboratories, Inc.

Drug Name: Escitalopram (Lexapro<sup>TM</sup>)

Supplement Type: Labeling supplement

Proposed Indication: Treatment of major depressive disorder

Date Submitted: 02/06/03

User Fee Due Date: 12/07/03

Final Review Completed: 10/31/03

Reviewer: Cara Alfaro, Pharm.D.

# CLINICAL REVIEW

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# Clinical Review for NDA 21-323

## Executive Summary

### I. Recommendations

#### A. Recommendation on Approvability

I recommend that the Division take an approvable action for supplemental NDA 21-323/SE8-007. In this labeling supplement, the Sponsor has submitted data from two clinical trials to add to the Clinical Efficacy Trials section of labeling and proposes to delete reference to racemic citalopram in this section of labeling. The data regarding the efficacy of Lexapro in the treatment of major depressive disorder, for which this SSRI already has an indication, is supported by the submitted clinical trials.

The Sponsor also included a study (SCT-MD-10) evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests. Proposed changes in labeling are supported by the findings from this study.

Several recommendations for changes in the Sponsor's proposed labeling are outlined in this review. In addition, SSRI class labeling has recently been finalized for discontinuation symptoms, pregnancy/nonteratogenic effects (neonatal withdrawal) and abnormal bleeding – these sections have also been incorporated into the Sponsor's proposed labeling.

The Division of Scientific Investigations has completed its site inspections. A final report was pending at the time this clinical review was completed.

### II. Summary of Clinical Findings

#### A. Brief Overview of Clinical Program

The Sponsor submitted data from two clinical trials to support changes in the Clinical Efficacy Trials section of labeling. Both clinical trials were 8-week studies in outpatients with major depressive disorder. Study 99001 was a fixed-dose study that included escitalopram 10 mg (n = 188) and placebo (n = 189). Study 99003 was a flexible-dose study that included escitalopram 10 – 20 mg (n = 155), citalopram 20 – 40 mg (n = 159) and placebo (n = 154). Neither of these clinical trials involved U.S. sites.

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In this submission, the Sponsor also included a study (SCT-MD-10) evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests.

#### **B. Efficacy**

The two clinical trials submitted support the efficacy of escitalopram 10 to 20 mg/day in the treatment of major depressive disorder. The primary efficacy endpoint was the change in MADRS total score (8 weeks compared to baseline) comparing escitalopram to placebo. The LOCF analysis for both trials showed statistical significance in favor of escitalopram ( $p = 0.002$  for both Studies 99001 and 99003); the OC findings were similar. The overall mean difference between escitalopram and placebo on the MADRS was 2.7 to 2.9 points.

#### **C. Safety**

Safety data from studies 99001 and 99003 were included in the original NDA ISS submitted on 3/23/01 and were reviewed at that time (Medical Officer: K. Brugge, MD). The only additional safety data in the current submission was that submitted for protocol SCT-MD-10, a study evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests in healthy volunteers. No deaths or serious adverse events occurred in this small study ( $n = 16$ ). Adverse events that occurred in this trial are described in current labeling.

#### **D. Dosing**

No changes to currently approved dosage and administration are proposed in this labeling supplement.

## CLINICAL REVIEW

### Clinical Review Section

#### Clinical Review

#### I. Introduction and Background

##### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Escitalopram (Lexapro<sup>TM</sup>) is the S-enantiomer of citalopram, a selective serotonin reuptake inhibitor (SSRI), and is approved for the treatment of major depressive disorder. The Sponsor has submitted clinical data from two clinical trials to add to the Clinical Efficacy Trials section of labeling and proposes to delete reference to racemic citalopram in this section of labeling.

No changes to currently approved dosage and administration are proposed in this labeling supplement.

##### B. State of Armamentarium for Indication(s)

Many medications from different pharmacological classes are available for the treatment of major depressive disorder, the SSRIs represent one class. In addition to escitalopram (Lexapro), other SSRIs that are currently approved for the treatment of major depressive disorder include: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil) and citalopram (Celexa). In the U.S., the SSRI fluvoxamine (Luvox) is approved for the treatment of obsessive-compulsive disorder only.

##### C. Important Milestones in Product Development

In a 4/22/98 letter, the Division informed the Sponsor that one single adequate and well-controlled efficacy trial in major depressive disorder would be sufficient to support an efficacy claim for the S-enantiomer of racemic citalopram (assuming that racemic citalopram had been shown to be effective in major depressive disorder).

The original NDA for escitalopram for the treatment of major depressive disorder was submitted on 3/23/01. This NDA included clinical trial data from four clinical studies: SCT-MD-01, SCT-MD-02, 99001 and 99003. Three of these four trials were considered positive (SCT-MD-02 was considered a failed study). In the original submission, the Sponsor did not include studies 99001 and 99003 in the ISE and the proposed labeling mentioned only one positive study (SCT-MD-01). Additionally, the Sponsor had not submitted statistical datasets for studies 99001 and 99003. In the 7/12/01 safety update, the Sponsor included the datasets for these studies with updated proposed labeling describing these studies. However, due to the late submission of this data and the fact that approval could be considered with the efficacy data from the single positive trial, this data was not reviewed by the statistician at that time. The Division suggested to the

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Sponsor to submit the results from these two studies in a post-action supplement if they wished to have them included in labeling.

The Division issued an approvable letter on 1/23/02. Escitalopram was approved for the treatment of major depressive disorder on 8/14/02 based on the results from one of the submitted clinical trials. Since studies 99001 and 99003 could not be fully evaluated due to the lack of available datasets at the time of original submission, approved labeling included reference to racemic citalopram: "The efficacy of LEXAPRO in the treatment of major depressive disorder was established, in part, on the basis of extrapolation from the established effectiveness of racemic citalopram, of which escitalopram is the active isomer." The Sponsor had submitted the safety data from studies 99001 and 99003, therefore these data had been reviewed when final approval was given.

The current labeling supplement was submitted on 2/6/03. The Sponsor proposes to describe studies 99001 and 99003 in labeling while deleting reference to racemic citalopram. The Sponsor also submitted study SCT-MD-10 evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests to support labeling changes primarily in the Precautions (interference with cognitive and motor performance) and Drug Interactions sections.

## **II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**

There are no chemistry or animal pharmacology/toxicology issues in this submission.

## **III. Human Pharmacokinetics and Pharmacodynamics**

Reference is made to approved NDA 21-323 for escitalopram for the treatment of major depressive disorder. In this submission, the Sponsor included a study (SCT-MD-10) evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests (pharmacodynamics). This study is reviewed in the Safety section of this clinical review.

## **IV. Description of Clinical Data and Sources**

### **A. Overall Data**

The Sponsor submitted data from two clinical trials to support changes in the Clinical Efficacy Trials section of labeling. Both clinical trials were 8-week studies in outpatients with major depressive disorder. Study 99001 was a fixed-dose study that included escitalopram 10 mg (n = 188) and placebo (n = 189). Study 99003 was a flexible-dose study that included escitalopram 10 – 20 mg (n =

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155), citalopram 20 – 40 mg (n = 159) and placebo (n = 154). Neither of these clinical trials involved U.S. sites.

In this submission, the Sponsor included a study (SCT-MD-10) evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests. This study is reviewed in the Safety section of this clinical review.

- B. Tables Listing the Clinical Trials**  
No supportive studies were included in this submission.
- C. Postmarketing Experience**  
N/A – labeling supplement
- D. Literature Review**  
N/A – labeling supplement
- E. Foreign Regulatory Review**  
N/A – labeling supplement

### V. Clinical Review Methods

#### A. How the Review was Conducted

This submission contained study reports for clinical trials 99001 and 99003 supporting efficacy in the treatment of major depressive disorder. Since the safety data had been submitted with the original NDA and reviewed, only the efficacy data was reviewed for this labeling supplement. No supportive trials were included in this submission.

Results of the analyses were compared with those conducted by the Sponsor. This reviewer consulted with reviewers from other disciplines including Biometrics and the Division of Scientific Investigations.

#### B. Overview of Materials Consulted in Review

The labeling supplement to NDA 21-323 (SE8-007) was a paper submission though the Sponsor also submitted study reports and datasets on CD. Requests for information throughout the review process were submitted electronically. Correspondences and clinical reviews for the original NDA submission were consulted to review regulatory issues and decisions made with respect to this supplement.

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#### **C. Overview of Methods Used to Evaluate Data Quality and Integrity**

Raw data were submitted to the Division of Biometrics via SAS transport files and analyzed according to the methods described in the Sponsor's protocol. The submission was also examined for internal consistency. DSI was consulted to inspect foreign sites that recruited subjects for the studies, these studies did not include any U.S. sites.

#### **D. Were Trials Conducted in Accordance with Accepted Ethical Standards**

The trial was conducted according to the ICH guideline for Good Clinical Practice.

#### **E. Evaluation of Financial Disclosure**

N/A – Labeling supplement

### **VI. Integrated Review of Efficacy**

#### **A. Brief Statement of Conclusions**

The two clinical trials submitted support the efficacy of escitalopram 10 to 20 mg/day in the treatment of major depressive disorder. The primary efficacy endpoint was the change in MADRS total score (8 weeks compared to baseline) comparing escitalopram to placebo. The LOCF analysis for both trials showed statistical significance in favor of escitalopram ( $p = 0.002$  for both Studies 99001 and 99003); the OC findings were similar. The overall mean difference between escitalopram and placebo on the MADRS was 2.7 to 2.9 points.

#### **B. General Approach to Review of the Efficacy of the Drug**

Efficacy data from the two clinical trials were reviewed in detail. The results obtained by the biometrics reviewer were compared with the Sponsor's efficacy analyses.

#### **C. Detailed Review of Trials by Indication**

Two clinical trials (99001 and 99003) were submitted to support labeling changes in the Clinical Efficacy Trials section of labeling for the treatment of major depressive disorder. Each trial is reviewed separately. The main difference between the two trials is that 99001 was a fixed-dose study of escitalopram and placebo and 99003 was a flexible-dose study of escitalopram, citalopram and placebo.

## CLINICAL REVIEW

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#### **C-1 Study 99001 – “A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg Lu 26-054 (escitalopram) in outpatients with major depressive disorder”**

This study was initiated on 8/27/99 and completed on 8/31/00. The study report was completed on 1/16/01.

##### **C-1.1 Investigators and Sites**

A list of investigators and sites may be found in Table C-1.1-A in the Appendix. A total of 40 centers in Canada (3), Estonia (4), France (27), the Netherlands (5) and the United Kingdom (1) recruited subjects in this multicenter study. No U.S. sites were used in this study.

##### **C-1.2 Objectives**

To compare the efficacy and safety of 10 mg escitalopram with placebo in outpatients with Major Depressive Disorder.

##### **C-1.3 Study Population**

This study enrolled generally healthy outpatients (18 – 65 years of age) with a DSM-IV diagnosis of Major Depressive Disorder. Subjects must have had a total score of at least 22 and not more than 40 on the MADRS at screening and baseline.

Exclusion criteria are listed in Table C-1.3-A in the Appendix. Briefly, subjects were excluded if they were at significant risk of suicide; met DSM-IV criteria for Mania or Bipolar Disorder, Schizophrenia or any psychotic disorder, Obsessive-Compulsive Disorder, current eating disorders, mental retardation or any pervasive developmental disorder or cognitive disorder; taken psychotropic drugs within specified time intervals prior to screening (including ECT); currently receiving psychotherapy or were citalopram nonresponders.

Subjects were to be withdrawn from the study if, among other criteria, they had a significant risk of suicide or  $\geq 5$  points on item 10 of the MADRS (5 is intermediate between 4 = suicidal thoughts without plan and 6 = suicidal plans) or if the MADRS total score  $\geq 40$ .

##### **C-1.4 Design**

This was a double-blind, placebo-controlled, fixed-dose, multicenter study. A one-week single-blind placebo run-in period preceded randomization. Subjects were randomized (1:1) to 10 mg escitalopram or placebo for 8 weeks. Study visits occurred at weeks 1, 2, 3, 4, 6, and 8. After completion of the study, subjects could continue in an open-label, 12-month extension phase or attend a follow-up visit 30 days later.

##### **C-1.5 Statistical Analysis Plan**

Per protocol, the primary efficacy analysis was the change from baseline to final assessment (LOCF) of the MADRS total score. The analysis was based on a general linear model for ANCOVA with factors for treatment group, center and treatment-by-center interaction and with baseline score as a covariate. Per

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protocol (section 7.6), an analysis plan describing the data sort-out and the planned statistical analysis plan in more detail was to be prepared by the Biostatistics Department prior to unblinding the study and analyzing the data. This analysis plan was included in the study report. Per study report, all centers that did not contribute to both treatment groups and did not contribute with at least 4 patients in LOCF analysis dataset were merged into a single collective center.

#### C-1.6 Assessments

The primary efficacy variable was the MADRS total score with the primary efficacy endpoint being the change from baseline to last assessment of the MADRS total score (LOCF). Secondary efficacy variables included the CGI-S and CGI-I scores (see Table C-1.6-A in the Appendix for secondary endpoints).

Screening and end-of-study safety assessments included medical/psychiatric history, adverse events, concomitant medications, physical examination, vital signs (sitting blood pressure and pulse, weight), ECG, and the following laboratory assessments:

Serum pregnancy test

Hematology: hemoglobin, hematocrit, red blood cells, white blood cells (total and differential), platelets

Clinical chemistry: total bilirubin, alkaline phosphatase, protein, ALT, AST, total, albumin, sodium, potassium, calcium (total), creatinine, glucose (non fasting)

Thyroid function tests: TSH

#### C-1.7 Subject Disposition

The following populations were defined by the Sponsor:

APRS = all patients randomized set: termed ITT population by reviewer

APTS = all patients treated set (received at least one dose): termed safety population by reviewer

FAS = full analysis set (at least one dose/one post baseline assessment): termed Modified ITT population by reviewer

PPS = per protocol set

Table C-1.7.1 Subject Populations

	Placebo	Escitalopram
ITT Population	189	191
Safety Population	189	191
Modified ITT Population	189	188

A total of 380 subjects were randomized (189 to placebo and 191 to escitalopram). Eighty-four percent of subjects (320/380) completed the study.

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Table C-1.7.2. Subject Disposition (Sponsor's Table)

### Panel 7 Withdrawals from Study by Primary Reason (APTS)

	Treatment Groups					
	PBO		ESC		Total	
	n	(%)	n	(%)	n	(%)
Patients Treated	189		191		380	
Patients Withdrawn	29	(15.3)	31	(16.2)	60	(15.8)
Primary Reason:						
Adverse Event(s)	2	(1.1)	9	(4.7)	11	(2.9)
Lack of efficacy	13	(6.9)	7	(3.7)	20	(5.3)
Non-compliance with study medication	0	(0.0)	0	(0.0)	0	(0.0)
Protocol violation	2	(1.1)	4	(2.1)	6	(1.6)
Withdrawal of consent	3	(1.6)	6	(3.1)	9	(2.4)
Lost to follow up	6	(3.2)	3	(1.6)	9	(2.4)
Administrative reason(s)	0	(0.0)	0	(0.0)	0	(0.0)
Other reason(s)	3	(1.6)	2	(1.0)	5	(1.3)

More specific reasons for “withdrawal of consent” and “lost to follow up” were not available due to limitations in the way the data was collected. Few subjects discontinued due to “other reasons” - since the proportions of these subjects were similar between groups, no further elaboration was requested from the Sponsor. The reasons for subject withdrawal from the clinical trial were fairly similar between the placebo and escitalopram groups with the exception that more subjects withdrew from the escitalopram group due to adverse events (4.7% vs. 1.1%) and from the placebo group due to lack of efficacy (6.9% vs. 3.7%). The differences in withdrawals between groups did not reach statistical significance.

The withdrawals due to adverse events in the placebo group included (n = 1 except where noted): amnesia, emotional lability and nausea (n = 1) and in the escitalopram group included alopecia, chest pain, constipation, ejaculation disorder, headache, insomnia, nausea (n = 3), vertigo (n = 2) and vision abnormal [subjects may have had more than one adverse event].

### C-1.8 Baseline Demographics/Severity of Illness

Table C-1.8.1 Subject Demographics (mean ? SD)

	Placebo (N = 189)	Escitalopram (N = 191)
Sex		
Female	147 (78%)	141 (74%)
Male	42 (22%)	50 (26%)
Race		
Caucasian	185 (98%)	188 (98%)
Black	0	1 (0.5%)
Asian	0	0
Other	4 (2%)	2 (1%)
Age (years)	40 ± 12	41 ± 11
Weight (kg)	69 ± 16	71 ± 17
Height (cm)	166 ± 8	167 ± 8
BMI (kg/m2)	25 ± 5	26 ± 6

Modified from Sponsor panels 8 and 9

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Table C-1.8.2 Baseline Severity of Illness

	Placebo (n = 189)	Escitalopram (N = 188)
MADRS Total Score		
Mean (SD)	29 (4)	29 (4)
Median	29	29
Range	21 – 40*	22 - 39
CGI-S		
Mean (SD)	4.4 (0.6)	4.4 (0.7)
Median	4	4
Range	3 - 6	3 - 6

Modified from Sponsor tables 18 and 29

\*Inclusion of subjects with MADRS total score = 21 and 40 were in violation of protocol

The inclusion criteria specified a minimum score (22) and maximum score (39) on the MADRS total score at baseline. The two treatment groups were similar with regard to baseline severity of illness as measured by the MADRS total score and the CGI –S.

Comorbid psychiatric diagnoses: approximately 20% of subjects in both groups had an ongoing psychiatric condition (other than MDD) at baseline. Unspecified anxiety was present in 12% of subjects in the placebo group and 7% of subjects in the citalopram group; insomnia was present in 12% of subjects in both groups.

### C-1.9 Concomitant Medications

Use of most concomitant psychotropic medications was not allowed during the clinical trial, details can be found in the exclusion criteria in Table C-1.3-A in the Appendix.

Concomitant use of benzodiazepines were allowed if used for insomnia “in a stabilized dose during the last 6 months or used episodically in the lower part of the recommended dose range”.

Per the Sponsor’s study report, in both treatment groups approximately 63% of subjects continued concomitant medication at baseline and 47% of subjects started concomitant medication after baseline. The Sponsor stated that there were no clinically relevant differences between the treatment groups.

This reviewer focused on concomitant medications that could confound efficacy results – specifically the use of benzodiazepines and other anxiolytics and antidepressants. Though the Sponsor provided a summary table for use of all concomitant medications (Listing A.8), this table included all recent and concomitant medications such that this reviewer had to evaluate each medication entry as to whether it was truly concomitant or not.

A total of 18% (35/189) in the placebo group and 21% (40/191) in the escitalopram group received concomitant medications, such as benzodiazepines and antidepressants, that could confound study results (see Table C-1.9-A in the Appendix). For many of these concomitant medications (60% in the placebo group and 40% in the escitalopram group), missing data regarding either the start

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date or duration of use precluded determination of duration of concomitant use. The majority of these concomitant medications were benzodiazepines, zolpidem or zopiclone (> 77% in both groups). Since similar proportions of subjects received these concomitant medications during the clinical trial, it is unlikely that this contributed to any difference in efficacy per the study results.

### C-1.10 Efficacy Results

#### C-1.10.1 Sponsor's Analysis

The primary efficacy endpoint was defined as the change in MADRS total score from baseline to week 8 (or last assessment) using LOCF with a modified ITT population (subjects receiving at least one dose of study medication with at least one post baseline assessment).

Adjusted mean changes in MADRS total scores for the LOCF and OC analyses are in Tables C-1.10.1.1 and C-1.10.1.2. The statistical model used was an ANCOVA with treatment and center as factors and baseline MADRS total score as a covariate.

Table C-1.10.1.1 LOCF Analysis: MADRS Total Score Adjusted Mean Change from Baseline

	Placebo (n = 189)		Escitalopram (n = 188)		Difference (95% CI)
	LS Mean	SE	LS Mean	SE	
Week 1	-4.3	0.39	-4.8	0.39	-0.5 (-1.5, 0.4), p = 0.26
Week 2	-6.8	0.51	-8.5	0.51	-1.8 (-3.0, -0.5), p = 0.0049
Week 3	-9.4	0.59	-13.1	0.59	-2.5 (-4.0, -1.1), p = 0.0006
Week 4	-11.3	0.63	-14.1	0.63	-2.8 (-4.4, -1.3), p = 0.0003
Week 6	-12.0	0.69	-15.5	0.68	-3.5 (-5.2, -1.8), p < 0.0001
Week 8	-13.6	0.69	-16.3	0.69	-2.7 (-4.3, -1.0), p = 0.0018

Constructed from SASS output in Study Report

Table C-1.10.1.2. OC Analysis: MADRS Total Score Adjusted Mean Change from Baseline

	Placebo			Escitalopram			Difference (95% CI)
	LS Mean	SE	n	LS Mean	SE	n	
Week 1	-4.3	0.41	185	-5.0	0.40	186	-0.7 (-1.7, 0.2), p = 0.141
Week 2	-6.9	0.52	174	-8.7	0.52	180	-1.9 (-3.1, -0.6), p = 0.004
Week 3	-9.7	0.59	172	-12.5	0.59	173	-2.8 (-4.2, -1.3), p < 0.001
Week 4	-12.1	0.60	169	-14.6	0.60	171	-2.5 (-3.9, -1.0), p = 0.001
Week 6	-12.8	0.68	162	-16.4	0.68	166	-3.6 (-5.3, -1.0), p < 0.001
Week 8	-14.7	0.64	159	-17.4	0.64	161	-2.7 (-4.3, -1.1), p = 0.001

From Sponsor Panels 16 and 17

The results for the LOCF and OC analyses were very similar with statistical separation occurring at week 2 and continuing until the end of the study.

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The results from selected secondary efficacy endpoints are in Tables C-1.10.1.1-A in the Appendix. In general, most of the secondary efficacy endpoints favored escitalopram over placebo.

#### **C-1.10.2 Division's Analysis**

The reviewing statistician, Yeh-Fong Chen, Ph.D., was able to replicate the LOCF and OC analyses of the Sponsor (see statistical review). No significant disparities arose during the statistical review of these two clinical trials.

The placebo effect was fairly significant in this clinical trial, at week 8 (LOCF) the MADRS total score decreased by 13.6 points in the placebo group versus 16.3 points in the escitalopram group. The separation between placebo and escitalopram on the MADRS total score at week 8 was only 2.7 points (LOCF). However, this difference was robust from a statistical perspective.

Subjects with a MADRS  $\geq 40$  were excluded from the trial, subjects achieving a total score  $\geq 40$  during the study were to be dropped from the study. Though the Sponsor stated that only one subject was enrolled with a MADRS  $\geq 40$  in violation of the protocol, a review of the individual MADRS scores found 5 subjects who had a MADRS  $\geq 40$  (at either screening or day 7) and were continued in the trial. Three of these subjects were in the escitalopram group and 2 were in the placebo group. Since inclusion of these subjects were similar between the two groups, no further analysis was performed to exclude these subjects.

#### **C-2 Study 99003 – “A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of escitalopram and citalopram in outpatients with major depressive disorder”**

This study was initiated on 9/15/99 and completed on 7/28/00. The study report was completed on 1/17/01.

##### **C-2.1 Investigators and Sites**

A list of investigators and sites may be found in Table C-2.1-A in the Appendix. A total of 69 centers in Belgium (3), Canada (3), Finland (10), France (22), Norway (8), Sweden (2), Switzerland (4), and the United Kingdom (17) recruited subjects in this multicenter study. No U.S. sites were used in this study.

##### **C-2.2 Objectives**

To compare the efficacy and safety of Lu 26-054 (escitalopram) independent of dose in the interval of 10 – 20 mg daily with that of placebo using citalopram (20 – 40 mg daily) as reference drug in outpatients with Major Depressive Disorder.

##### **C-2.3 Study Population**

This study enrolled generally healthy outpatients (18 – 65 years of age) with a DSM-IV diagnosis of Major Depressive Disorder. Subjects must have a score of at least 22 and not more than 40 on the MADRS total score at screening and

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baseline. The inclusion and exclusion criteria are the same as that for study 99001 (see section C-1.3 and C-1.3-A in the Appendix). Similar to study 99001, subjects were to be withdrawn from the study if, among other criteria, they had a significant risk of suicide or  $\geq 5$  points on item 10 of the MADRS (5 is intermediate between 4 = suicidal thoughts without plan and 6 = suicidal plans) or if the MADRS total score  $\geq 40$ .

### C-2.4 Design

This was a double-blind, placebo-controlled, flexible-dose, multicenter study. A one-week single-blind placebo run-in period preceded randomization. Subjects were randomized (1:1:1) to 10-20 mg escitalopram, 20-40 mg citalopram or placebo for 8 weeks. Subjects initially received either 10 mg of escitalopram or 20 mg of citalopram. Doses could be increased at week 4 or 6 to 20 of escitalopram or 40 mg of citalopram if the response had been unsatisfactory (no improvement in CGI-S from baseline or CGI-S score  $\geq 5$ ) or depression was "aggravated" (increase in CGI-S compared with score at previous assessment). Study visits occurred at weeks 1, 2, 3, 4, 6, and 8. After completion of the study, subjects could continue in an open-label, 12-month extension phase or attend a follow-up visit 30 days later.

### C-2.5 Statistical Analysis Plan

Same as per protocol 99001.

### C-2.6 Assessments

Same as per protocol 99001.

### C-2.7 Subject Disposition

Table C-2.7.1. Subject Populations

	Placebo	Citalopram	Escitalopram
ITT Population	154	161	156
Safety Population	154	160	155
Modified ITT Population	154	159	155

A total of 471 subjects were randomized (154 placebo, 161 citalopram and 156 escitalopram). Ninety-three percent of subjects (437/471) completed the study (> 90% completed all groups).

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Table C-2.7.2. Subject Disposition (Sponsor's Table)

**Panel 7 Withdrawals from Study by Primary Reason (APTS)**

	Treatment Groups							
	PBO		CIT		ESC		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients Treated	154		160		155		469	
Patients Withdrawn	15	( 9.7)	8	( 5.0)	9	( 5.8)	32	( 6.8)
Primary Reason:								
Adverse Event(s)	4	( 2.6)	6	( 3.8)	4	( 2.6)	14	( 3.0)
Lack of efficacy	5	( 3.2)	1	( 0.6)	0	( 0.0)	6	( 1.3)
Non-compliance with study medication	0	( 0.0)	0	( 0.0)	0	( 0.0)	0	( 0.0)
Protocol violation	1	( 0.6)	0	( 0.0)	2	( 1.3)	3	( 0.6)
Withdrawal of consent	1	( 0.6)	0	( 0.0)	1	( 0.6)	2	( 0.4)
Lost to follow up	2	( 1.3)	1	( 0.6)	2	( 1.3)	5	( 1.1)
Administrative	0	( 0.0)	0	( 0.0)	0	( 0.0)	0	( 0.0)
Other reason(s)	2	( 1.3)	0	( 0.0)	0	( 0.0)	2	( 0.4)

The reasons for subject withdrawal from the clinical trial were fairly similar between the placebo, citalopram and escitalopram groups with the exception that more subjects withdrew from the placebo group due to lack of efficacy (3.2% vs. 0 – 0.6%).

Withdrawals due to adverse events - subjects may have had more than one adverse event (n = 1 unless otherwise noted):

Placebo: alcohol problem, depression aggravated (could have also been coded as lack of efficacy), nervousness and neurosis.

Citalopram: fetal death, dermatitis, dyspnea, hallucination, headache, hypertension, migraine, nausea (n = 2), pregnancy unintended and vision abnormal. The fetal death was a spontaneous miscarriage and was reported as a serious adverse event.

Escitalopram: abdominal pain, conjunctivitis, diarrhea, ejaculation disorder, malaise, nausea, pruritis and vision abnormal.

### C-2.8 Baseline Demographics/Severity of Illness

Table C-2.8.1 Subject Demographics (mean ? SD)

	Placebo (N = 154)	Citalopram (N = 160)	Escitalopram (N = 155)
Sex			
Female	111 (72%)	111 (69%)	116 (75%)
Male	43 (28%)	49 (31%)	39 (25%)
Race			
Caucasian	154 (100%)	156 (97%)	153 (99%)
Black	0	0	0
Asian	0	2 (1.3%)	2 (1.3%)
Other	0	2 (1.3%)	0
Age (years)	43 ± 12	44 ± 11	43 ± 11
Weight (kg)	76 ± 18	74 ± 14	71 ± 16
Height (cm)	168 ± 9	167 ± 9	166 ± 9
BMI (kg/m <sup>2</sup> )	27 ± 6	26 ± 5	26 ± 6

Modified from Sponsor Panels 8 and 9

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Table C-2.8.2 Baseline Severity of Illness

	Placebo (N = 154)	Citalopram (N = 159)	Escitalopram (N = 155)
MADRS Total Score			
Mean (SD)	29 ± 4	29 ± 4	29 ± 4
Median	28	29	29
Range	22 - 40*	22 - 39	20 - 39
CGI-S			
Mean (SD)	4.2 ± 0.8	4.3 ± 0.7	4.3 ± 0.8
Median	4	4	4
Range	2 - 6	2 - 6	2 - 6

Modified from Sponsor tables 19 and 30

\*Inclusion of subject with MADRS total score = 40 was in violation of protocol

The inclusion criteria specified a minimum score (22) and maximum score (39) on the MADRS total score at baseline. The two treatment groups were similar with regard to baseline severity of illness as measured by the MADRS total score and the CGI -S.

Comorbid psychiatric diagnoses: approximately 10-14% of subjects in all groups had an ongoing psychiatric condition (other than MDD) at baseline. Unspecified anxiety was present in 6% of subjects in the citalopram group compared to 3% and 1% in the placebo and escitalopram groups respectively.

### C-2.9 Concomitant Medications

Similar to the evaluation of study 99001, this reviewer focused on concomitant medications that could confound efficacy results – specifically the use of benzodiazepines and other anxiolytics and antidepressants.

A total of 28% (43/154) in the placebo group, 29% (46/160) in the citalopram group and 25% (39/155) in the escitalopram group received concomitant medications, such as benzodiazepines and antidepressants, that could confound study results (see Table C-2.9-A in the Appendix). For many of these concomitant medications (86% in the placebo group, 78% in the citalopram group and 77% in the escitalopram group), missing data regarding either the start date or duration of use precluded determination of duration of concomitant use. The majority of these concomitant medications were benzodiazepines, zolpidem or zopiclone (> 72% in all groups). Since similar proportions of subjects received these concomitant medications during the clinical trial, it is unlikely that this contributed to any difference in efficacy per the study results.

### C-2.10 Efficacy Results

#### C-2.10.1 Sponsor's Analysis

At week 8, the mean dose was 28.4 ± 9.8 mg/day in the citalopram group and 14.0 ± 4.8 mg/day in the escitalopram group.

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Table C-2.10.1.1. LOCF Analysis: MADRS Total Score Adjusted Mean Change from Baseline

	Placebo (n = 154)		Citalopram (n = 159)		Escitalopram (n = 155)		Difference (95% CI)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	
Week 1	-3.4	0.39	-4.0	0.39	-4.4	0.39	Cit-PC: -0.6 (-1.7, 0.4); p = 0.23 Esc-PC: -1.0 (-2.0, 0.04); p = 0.06
Week 2	-6.6	0.51	-7.2	0.51	-8.0	0.51	Cit-PC: -0.7 (-2.1, 0.7); p = 0.32 Esc-PC: -1.5 (-2.9, -0.1); p = 0.03
Week 3	-8.4	0.57	-9.3	0.57	-10.4	0.57	Cit-PC: -0.9 (-2.5, 0.6); p = 0.24 Esc-PC: -2.0 (-3.5, -0.4); p = 0.01
Week 4	-8.6	0.62	-10.4	0.62	-11.5	0.62	Cit-PC: -1.9 (-3.5, -0.2); p = 0.03 Esc-PC: -2.9 (-4.6, -1.2); p = 0.0007
Week 6	-10.8	0.64	-12.1	0.64	-13.5	0.64	Cit-PC: -1.3 (-3.0, 0.4); p = 0.14 Esc-PC: -2.7 (-4.5, -1.0); p = 0.0023
Week 8	-12.2	0.67	-13.7	0.67	-15.1	0.67	Cit-PC: -1.5 (-3.3, 0.33); p = 0.109 Esc-PC: -2.9 (-4.7, -1.1); p = 0.002

Constructed from SASS output in Study Report

Table C-2.10.1.2. OC Analysis: MADRS Total Score Adjusted Mean Change from Baseline

	Placebo			Citalopram			Escitalopram			Difference (95% CI)
	LS Mean	SE	n	LS Mean	SE	n	LS Mean	SE	n	
Week 1	-3.1	0.41	149	-3.9	0.40	154	-4.4	0.40	154	Cit-PC: -0.8 (-1.9, 0.3) p = 0.16 Esc-PC: -1.3 (-2.4, -0.2) p = 0.023
Week 2	-6.8	0.51	140	-7.5	0.49	150	-8.2	0.50	146	Cit-PC: -0.7 (-2.1, 0.6) p = 0.304 Esc-PC: -1.4 (-2.8, -0.1) p = 0.037
Week 3	-8.8	0.59	141	-9.7	0.58	151	-10.6	0.60	143	Cit-PC: -0.9 (-2.5, 0.7) p = 0.264 Esc-PC: -1.8 (-3.4, -0.2) p = 0.029
Week 4	-9.1	0.63	144	-10.5	0.62	154	-11.8	0.63	145	Cit-PC: -1.4 (-3.1, 0.2) p = 0.095 Esc-PC: -2.8 (-4.5, -1.1) p = 0.002
Week 6	-11.2	0.63	145	-12.6	0.63	148	-13.7	0.63	144	Cit-PC: -1.4 (-3.1, 0.3) p = 0.105 Esc-PC: -2.6 (-4.3, -0.8) p = 0.003
Week 8	-13.5	0.66	138	-14.5	0.64	150	-15.9	0.64	145	Cit-PC: -1.0 (-2.7, 0.7) p = 0.252 Esc-PC: -2.3 (-4.1, -0.6) p = 0.009

From Sponsor Panels 15 and 16

The results for the LOCF and OC analyses were very similar with statistical separation occurring at week 2 (week 1 for OC) and continuing until the end of the study.

The results from selected secondary efficacy endpoints are in Tables C-2.10.1.1-A in the Appendix. In general, most of the secondary efficacy endpoints favored escitalopram over placebo.

#### C-2.10.2 Division's Analysis

The placebo effect was fairly significant in this clinical trial, at week 8 (LOCF) the MADRS total score decreased by 12.2 points in the placebo group versus 15.1

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points in the escitalopram group. The separation between placebo and escitalopram on the MADRS total score at week 8 was only 2.9 points (LOCF). However, this difference was robust from a statistical perspective.

Yeh-Fong Chen, the statistical reviewer for this submission, was able to duplicate the Sponsor's results for all efficacy endpoints for LOCF and OC datasets. As in study 99001, this reviewer reviewed the datasets for inclusion of subjects with MADRS  $\geq 40$ . Since only two subjects were identified meeting this criteria (1-placebo, 1-citalopram), a separate analysis excluding these subjects was not performed.

#### D. Efficacy Conclusions

The Sponsor submitted data from two clinical trials to support changes in the Clinical Efficacy Trials section of labeling. Both clinical trials were 8-week studies in outpatients with major depressive disorder. Study 99001 was a fixed-dose study that included escitalopram 10 mg (n = 188) and placebo (n = 189). Study 99003 was a flexible-dose study that included escitalopram 10 – 20 mg (n = 155), citalopram 20 – 40 mg (n = 159) and placebo (n = 154). Neither of these clinical trials involved U.S. sites.

The two clinical trials submitted support the efficacy of escitalopram 10 to 20 mg/day in the treatment of major depressive disorder. The primary efficacy endpoint was the change in MADRS total score (8 weeks compared to baseline) comparing escitalopram to placebo. The LOCF analysis for both trials showed statistical significance in favor of escitalopram (p = 0.002 for both Studies 99001 and 99003); the OC findings were similar. The overall mean difference between escitalopram and placebo on the MADRS was 2.7 to 2.9 points.

## VII. Integrated Review of Safety

#### A. Brief Statement of Conclusions

Safety data from studies 99001 and 99003 were included in the original NDA ISS submitted on 3/23/01 and were reviewed at that time (Medical Officer: K. Brugge, MD). The only additional safety data in the current submission was that submitted for protocol SCT-MD-10, a study evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests in healthy volunteers. No deaths or serious adverse events occurred in this small study (n = 16). Adverse events that occurred in this trial are described in current labeling.

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- B. Description of Patient Exposure**  
See Clinical Review of original NDA.
- C. Methods and Specific Findings of Safety Review**  
See Clinical Review of original NDA.

#### **C-3 Study SCT-MD-10 – “Placebo-controlled, crossover study of the psychomotor effects of escitalopram with and without alcohol co-administration”**

This study was initiated on 4/26/01 and completed on 3/27/02. The study report was completed on 12/5/02.

##### **C-3.1 Investigators and Sites**

This study was performed at one site, Southern California Research Institute. The principal investigator was Candace Jeavons Wilkinson, Ph.D.

##### **C-3.2 Objectives**

To evaluate the effects of escitalopram on cognitive and psychomotor function and its interaction with alcohol in healthy volunteers.

##### **C-3.3 Study Population**

This study enrolled healthy male or female volunteers 21-45 years of age within 15% of their ideal body weight. Subjects had to report social use of alcohol which classified them as moderate or heavy users on the Quality Frequency Variability alcohol use questionnaire. Among the exclusion criteria were consuming alcohol within 72 hours prior to screening, using prohibited medications within 2 weeks of baseline (most medications considered prohibited, some episodic use of certain classes allowed), or a history of drug or alcohol abuse within the last 5 years (see Table C-3.3-A in the Appendix for full exclusion criteria).

##### **C-3.4 Design**

This was a double-blind, placebo-controlled, four-way crossover study comparing the effects of 10 mg escitalopram to placebo with and without coadministration of alcohol (0.80g/kg) on psychomotor and cognitive function. Four blinded treatments were administered at one-week intervals over a 3-week period: escitalopram and alcohol, escitalopram and placebo alcohol, placebo and alcohol and placebo and placebo alcohol. Alcohol/placebo alcohol was administered approximately 3 hours after administration of escitalopram/placebo in three separate doses using a paced drinking rate at 10-minute intervals.

##### **C-3.5 Statistical Analysis Plan**

Per protocol, all analyses were based on the completer population. All tests were two-sided with a 5% significance level. The protocol did not use a composite

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overall score for the psychomotor test battery (see assessments), but rather evaluated each psychomotor test separately (change from baseline). A statistical analysis plan which was finalized on 6/12/02 was provided in Appendix VI of the study report. Per the statistical analysis plan, the effects of escitalopram and its interaction with alcohol were to be tested using a two-way ANOVA model with sequence, subject within sequence, treatment and period effects. The following treatment comparisons were to be tested: escitalopram + placebo alcohol versus placebo + placebo alcohol; placebo + alcohol versus placebo + placebo alcohol; and escitalopram + alcohol versus placebo + alcohol. The statistical analysis plan did not change the analyses specified in the protocol.

Treatment conditions:

	Study Medication	Alcohol Condition
Treatment A (combination)	10 mg escitalopram	0.80 g/kg alcohol
Treatment B (escitalopram)	10 mg escitalopram	Placebo
Treatment C (alcohol)	Placebo	0.80 g/kg alcohol
Treatment D (placebo)	Placebo	Placebo

### C-3.6 Assessments

Efficacy:

Psychomotor Test Battery (9 tests)– Choice reaction time (psychomotor speed), driving test, shopping list task (memory), digit symbol (visuospatial praxis), serial sevens (attention), finger tapping (motor speed), field sobriety test, visual analog scales for sedation/confusion/euphoria/intoxication, investigator assessment for coordination/speech/sedation.

Safety: Medical/psychiatric history, physical exam, vital signs, ECG and laboratory evaluations including serum pregnancy test, urine drug screen, hematology (WBC w/ differential, erythrocyte count, hemoglobin, hematocrit, platelets, RBC indices), chemistry (sodium, potassium, calcium, chloride, glucose, BUN, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, ALT, AST, cholesterol) and urinalysis.

The WHOART dictionary was used for coding adverse events.

Blood alcohol levels were also assessed via a breath samples obtained at timed intervals up to 3 hours after alcohol ingestion.

### C-3.7 Subject Disposition

A total of 19 subjects were randomized, 16 (84.2%) completed the study. The reasons for discontinuation were adverse events (n = 2) and protocol violation (n = 1).

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### C-3.8 Baseline Demographics

Table C-3.8. Subject Demographics (Sponsor's Table)

Panel 9. Demographic Characteristics

		D-C-A-B (N=6)	A-D-B-C (N=4)	B-A-C-D (N=4)	C-B-D-A (N=5)	Total
Age, years	Mean (SD)	23.2 (2.5)	23.3 (2.1)	21.8(1.5)	24.0(4.1)	23.1 (2.7)
	Median	22.5	23.0	21.0	22.0	22.0
	Min, Max	21,28	21,26	21,24	21,31	21,31
Race, n (%)	Caucasian	5 (83.3)	4 (100)	2 (50.0)	5 (100)	16 (84.2)
	Noncaucasian	1 (16.7)	0	2 (50.0)	0	3 (15.8)
Weight, lbs	Mean (SD)	187.3 (21.4)	160.0 (29.2)	167.3 (30.5)	175.6 (23.8)	174.2 (25.8)
	Median	184.0	170.5	161.0	165.0	175
	Min, Max	156, 212	117, 182	140,207	152, 210	117, 212

Safety population.

Cross-reference: Table 2.1 and Appendix IX, Listing 2.

### C-3.9 Concomitant Medications

A total of 9/19 subjects received concomitant medications during the study, similar percentages during each treatment condition. The most frequently used concomitant medications were analgesics, antiinflammatory drugs and vitamins.

### C-3.10 Efficacy Results

#### C-3.10.1 Sponsor's Analysis

#### Blood Alcohol Concentration (BAC)

Though it is unlikely that blood alcohol concentrations would vary between treatment conditions due to the cross-over design of this protocol (unless a drug interaction were present), these concentrations were obtained and analyzed for differences.

Table C-3.10.1.1. Mean (SD) Blood Alcohol Concentration Assessments

	Escitalopram + Alcohol (n = 16)	Alcohol (n = 16)	p-value
BAC AUC	0.32 ± 0.04	0.34 ± 0.05	0.08
BAC 0.5 hr	0.07 ± 0.02	0.08 ± 0.02	0.03
BAC 1 hr	0.08 ± 0.009	0.08 ± 0.001	0.74
BAC 1.5 hr	0.08 ± 0.006	0.08 ± 0.008	0.88
BAC 2 hr	0.07 ± 0.007	0.07 ± 0.007	0.13
BAC 3 hr	0.06 ± 0.008	0.05 ± 0.007	0.34

From Sponsor Tables 10.1 and 10.2

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### Cognitive and Psychomotor Battery

#### Driving Test

No differences were noted between escitalopram and placebo for any of the driving parameters. Statistically significant decrements in performance were noted in the alcohol treatment condition compared to placebo, no further decrements were noted in the escitalopram + alcohol (combination) treatment condition. Though not statistically significant ( $p = 0.28$ ), it appears that the number of collisions was higher in the escitalopram + alcohol compared to the alcohol treatment condition (2.4 vs. 1.5); though the escitalopram treatment condition had more variability.

Table C-3.10.1.2. Driving Test: Mean Change (SD) from Baseline (Sponsor's Table)

Panel 10. Mean Change (SD) from Baseline in the Driving Test

	Combination (A) (N=16)	Alcohol (C) (N=16)	Escitalopram (B) (N=16)	Placebo (D) (N=16)
Sum of Driving Errors	6.1 (8.48)	5.4* (5.34)	-0.5 (2.61)	0.3 (4.16)
Speed Exceedances	3.3 (4.51)	3.4* (3.58)	-0.1 (1.91)	0.4 (2.68)
Collisions	2.4 (4.56)	1.5* (2.42)	-0.4 (1.55)	-0.3 (1.20)
Off Road Accidents	0.3 (1.08)	0.3 (0.70)	-0.1 (0.25)	0.0 (0.37)
Traffic Light Tickets	0.1 (1.00)	0.2 (1.38)	0.1 (1.18)	0.1 (1.71)
Lane Position Deviations	0.2 (0.11)	0.2** (0.21)	0.0 (0.19)	-0.0 (0.12)

\*  $p \leq 0.05$  in ANOVA comparison between alcohol and placebo treatments

\*\*  $p \leq 0.001$  in ANOVA comparison between alcohol and placebo treatments

Completer population

Cross-reference: Tables 3.1, and Appendix IX, Listing 6

#### Choice Reaction Time

Escitalopram versus alcohol approached significance ( $p = 0.09$ ), escitalopram not different from placebo ( $p = 0.40$ ).

Table C-3.10.1.3. Choice Reaction Time: Mean (SD) and Median Change from Baseline

	Combination (A) (N = 16)	Alcohol (C) (N = 16)	Escitalopram (B) (N = 16)	Placebo (D) (N = 16)
Reaction Time (msec)				
Mean (SD)	47.4 (131)*	61.6 (122)**	14.5 (85)	-8.4 (67)
Median	20	60	12	-2.5

\* $p = 0.05$ , combination versus placebo

\*\* $p = 0.01$ , alcohol versus placebo

#### Shopping List Tasks

No differences were noted between escitalopram and placebo for any of the shopping list tasks. Statistically significant decrements in performance were noted in the alcohol treatment condition compared to placebo, no further

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decrements were noted in the escitalopram + alcohol (combination) treatment condition. During the alcohol treatment condition, subjects performed worse compared to the escitalopram ( $p = 0.0001$ ) and placebo ( $p = 0.0001$ ) conditions. Similar findings were apparent during the escitalopram + alcohol treatment condition.

### C-3.10.1.4. Shopping List Tasks: Mean (SD) Change from Baseline (Sponsor's Table)

Panel 11. Mean Change (SD) from Baseline in Shopping List Tasks

	Combination (A) (N=16)	Alcohol (C) (N=16)	Escitalopram (B) (N=16)	Placebo (D) (N=16)
# Correct Immediate Recalls	-10.4 (7.41)	-11.9** (10.45)	-0.7 (6.17)	-1.4 (6.50)
# Correct Delayed Recalls	-2.5 (2.42)	-2.9** (2.69)	0.0 (1.75)	-0.2 (2.37)
# Intrusions	1.5 (1.93)	1.4 (2.50)	0.6 (1.26)	1.3 (1.91)

\*\*  $p \leq 0.001$  in ANOVA comparison of alcohol and placebo treatments  
 Completer population  
 Cross-reference: Table 3.3 and Appendix IX, Listing 8

### Digit Symbol Test

No differences were noted between escitalopram and placebo for the number of correct responses on the digit symbol test. Statistically significant decrements in performance were noted in the alcohol treatment condition compared to all other treatment conditions *including* the combination treatment condition.

Table C-3.10.1.5. Mean (SD) Change from Baseline in Digit Symbol Test

	Combination (A) (N = 16)	Alcohol (C) (N = 16)	Escitalopram (B) (N = 16)	Placebo (D) (N = 16)
Digit Symbol Test (# correct)	-3.4 (4.7)*	-7.2 (4.8)**	3.7 (5.7)	1.6 (6.3)

\* $p = 0.001$  (vs. escitalopram), 0.01 (alcohol), 0.001 (placebo)  
 \*\* $p = 0.0001$  (vs. escitalopram and placebo), 0.01 (combination)

### Serial 7's Test

No differences were noted between escitalopram and placebo for the number of correct responses on the serial 7's test. Statistically significant decrements in performance were noted in the alcohol treatment condition compared to all other treatment conditions *including* the combination treatment condition. Decrements in performance were also noted in the escitalopram + alcohol treatment condition compared to placebo ( $p = 0.03$ ) and trending towards significance compared to escitalopram ( $p = 0.09$ ).

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Table C-3.10.1.6. Serial 7s: Mean (SD) Change from Baseline (Sponsor's Table)

Panel 12. Mean Change (SD) from Baseline in the Serial Sevens Test

	Combination (A) (N=16)	Alcohol (C) (N=16)	Escitalopram (B) (N=16)	Placebo (D) (N=16)
# Correct	-0.2 † (2.10)	-1.6***† (2.34)	0.9 (3.36)	1.3 (2.02)
# Incorrect	0.6 (0.96)	0.2 (1.05)	0.1 (1.20)	-0.2 (1.17)

† p ≤ 0.05 in ANOVA comparison between combination and alcohol.

\*\* p ≤ 0.001 in ANOVA comparison between alcohol and placebo

Completer population

Cross-reference: Table 3.5 and Appendix IX, Listing 10

### Finger Tapping

Interestingly, during the escitalopram treatment condition subjects performed better than during the placebo condition ( $p = 0.005$ ). During the placebo treatment condition, subjects appeared to perform (numerically) worse compared to the combination condition ( $p = 0.26$ ). The Sponsor did not make further comments regarding this finding. No differences were noted in the alcohol versus placebo treatment conditions ( $p = 0.19$ ).

Table C-3.10.1.7. Mean (SD) Change from Baseline in Finger Tapping Test

	Combination (A) (N = 16)	Alcohol (C) (N = 16)	Escitalopram (B) (N = 16)	Placebo (D) (N = 16)
Number of Taps	3.3 (6.4)*	0.17 (6.2)**	5.6 (6.2)***	1.9 (5.7)

\*p = 0.02 versus alcohol

\*\*p = 0.02 (versus combination) and 0.0001 (escitalopram)

\*\*\*p = 0.005 versus placebo

### Field Sobriety

No differences were noted between escitalopram and placebo for any of the driving parameters. Statistically significant decrements in performance were noted in the alcohol treatment condition compared to placebo, no further decrements were noted in the escitalopram + alcohol (combination) treatment condition.

Table C-3.10.1.8. Mean (SD) Change from Baseline in Field Sobriety Score

	Combination (A) (N = 16)	Alcohol (C) (N = 16)	Escitalopram (B) (N = 16)	Placebo (D) (N = 16)
Score	4.7 (2.9)*	4.9 (2.8)*	0.2 (1.0)	0.06 (0.8)

\*p = 0.0001 versus escitalopram and placebo

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### Visual Analog Scale

Table C-3.10.1.9. Visual Analog Scale: Mean (SD) Change from Baseline (Sponsor's Table)

Panel 13. Mean Change (SD) from Baseline on the Visual Analog Scale

	Combination (A) (N=16)	Alcohol (C) (N=16)	Escitalopram (B) (N=16)	Placebo (D) (N=16)
<b>Visual Analog Scale</b>				
Sedation Score	12.0 (29.53)	9.4 (31.68)	10.6 (28.81)	4.8 (28.30)
Confusion Score	4.3 (10.90)	2.3 (5.78)	1.8 (5.88)	-0.7 (2.52)
Euphoria Score	-5.4 (16.48)	-1.6 (19.59)	-2.1 (14.19)	-2.4 (10.33)
Intoxication Score	56.3 (18.68)	51.3** (21.26)	6.3 (8.97)	0.7 (1.49)
<b>Investigator Assessments</b>				
Coordination Score	18.6 (16.44)	17.8** (14.49)	1.0 (8.45)	1.3 (6.29)
Speech Score	10.6 (12.82)	16.3** (16.20)	1.9 (7.36)	-0.4 (1.54)
Sedation Score	17.7 (15.50)	20.4** (14.15)	5.8 (10.89)	5.3 (12.51)

\*\* p<0.001 in ANOVA comparison between alcohol and placebo  
Completer population  
Cross-reference: Table 3.8, Table 3.9 and Appendix IX, Listings 13-14.

Table C-3.10.1.10. Summary Table for Cognitive and Psychomotor Assessments

	Escitalopram versus Placebo	Escitalopram + Alcohol versus Alcohol Treatment Condition
Driving Test	No differences	Similar decrements between groups compared to placebo
Choice Reaction Time	No differences	Similar decrements between groups compared to placebo
Shopping List	No differences	Similar decrements between groups compared to placebo
Digit Symbol Test	No differences	Decrements compared to placebo, E+A less than A
Serial 7's	No differences	Decrements compared to placebo, E+A less than A
Finger Tapping	Improvement vs. placebo	No decrements compared to placebo, E+A better than A
Field Sobriety	No differences	Similar decrements between groups compared to placebo
Visual Analog Scale – Self-rated	No differences	No decrements compared to placebo: sedation, euphoria Similar decrements between groups compared to placebo: confusion, intoxication
Visual Analog Scale - Investigator	No differences	Similar decrements between groups compared to placebo: coordination, speech, sedation

### C-3.10.2 Division's Analysis

No separate analysis was performed by the Division.

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### C-3.11 Deaths and Serious Adverse Events

No deaths or serious adverse events were reported during the conduct of the study.

### C-3.12 Discontinuations Due to Adverse Events

Two subjects discontinued due to adverse events (Table C-3.12). The subject with the “inflicted injury” experienced a right ankle fracture.

Table C-3.12. Discontinuations due to Adverse Events (Sponsor’s Table)

Panel 14. List of Subjects who Discontinued due to Adverse Events

Subject Number	Age	Treatment Sequence	Previous Treatment	AE Start Day	Preferred Term	Severity	Relationship to Study Drug
01	21	D-C-A-B	C	0	Nausea	Moderate	Related
				0	Vomiting	Mild	Related
				0	Somnolence	Moderate	Related
17	28	D-C-A-B	D	3	Inflicted Injury	Severe	Not Related

A= Escitalopram/Alcohol, B= Escitalopram/Placebo Alcohol,

C= Placebo/Alcohol, D= Placebo/Placebo Alcohol

\* AE start day = AE start date- previous treatment date

Safety population

Cross-reference: Table 4.3

### C-3.13 Adverse Events

Treatment-emergent adverse events occurring in > 10% of subjects in any treatment group are listed in Table C-3.13 (> 10% => 1 subject/group). Adverse events occurring more commonly in the escitalopram + alcohol (combination) treatment condition compared to the escitalopram or alcohol alone condition included somnolence, nausea and paresthesia. All adverse events were reviewed and no unexpected events were noted.

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Table C-3.13. Adverse Events Occurring in > 10% of Subjects in Any Treatment Condition (Sponsor's Table)

Panel 15. Most Frequently Reported Treatment Emergent Adverse Events (>10% of Subjects After Any Treatment)

	Number (%) of Subjects			
	Combination (A) (N=16)	Alcohol (C) (N=18)	Escitalopram (B) (N=16)	Placebo (D) (N=18)
Subjects with at least 1 TEAE	11 (68.8)	14 (77.8)	9 (56.3)	9 (50.0)
Somnolence	11 (68.8)	10 (55.6)	5 (31.3)	4 (22.2)
Nausea	4 (25.0)	1 (5.6)	2 (12.5)	0
Headache	2 (12.5)	2 (11.1)	2 (12.5)	2 (11.1)
Paraesthesia	2 (12.5)	0	1 (6.3)	0

Safety population

Cross-reference: Table 4.4 and Appendix IX, Listing 16

### C-3.14 Laboratory/Vital Signs/ECG Assessments

#### Clinical Laboratory Assessments

Two subjects had changes in clinical laboratory assessments that met Sponsor criteria for potentially clinically significant – both subjects had 2+ glucose in their urine (one in escitalopram + alcohol condition and one in alcohol condition). Laboratory assessments were performed at baseline and at end of study, labs were not obtained at the end of each treatment condition.

#### Vital Signs

No subjects experienced adverse events related to changes in vital signs. Vital signs were obtained once pre-dose and once post-dose (approximately 6 hrs after escitalopram/placebo or 3 hours after alcohol/placebo).

Table C-3.14. Mean Changes in Vital Signs

	Mean Change Systolic BP (mmHg)	Mean Change Diastolic BP (mmHg)	Mean Change Pulse (bpm)
Placebo	6.2	-1.9	5.4
Escitalopram	7.8	-0.9	7.1
Alcohol	0.4	-8.8	13.7
Escitalopram + Alcohol	6.1	-7.0	11.4

#### ECG Assessments

ECGs were obtained at baseline and end of study, assessments were not performed after each treatment condition. Most subjects had a decrease in QTc after receiving study drug. Two subjects had an increase in QTc > 30msec, one subject who received escitalopram as the last treatment condition had an increase of 42 msec and another who received placebo as the last treatment condition had an increase of 47 msec.

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#### C-3.15 Proposed Labeling

The Sponsor has proposed labeling based on results from Study SCT-MD-10. Prior information regarding use of racemic citalopram and alcohol were already in approved labeling, the Sponsor is proposing to replace racemic citalopram with escitalopram:

#### Precautions:

##### Interference with Cognitive and Motor Performance

In ~~a study studies~~ in normal volunteers, LEXAPRO 10 mg/day ~~racemic citalopram in doses of 40 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.

#### Information for Patients:

In ~~a study studies~~ in normal volunteers, LEXAPRO 10 mg/day ~~racemic citalopram in doses of 40 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 ~~citalopram~~ 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.

#### Drug Interactions:

Alcohol - Although LEXAPRO ~~racemic citalopram~~ 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.

#### D. Adequacy of Safety Testing

See Clinical Review of original NDA.

#### E. Summary of Critical Safety Findings and Limitations of Data

See Clinical Review of original NDA.

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### VIII. Dosing, Regimen, and Administration Issues

No changes in dosing, regimen or administration were proposed in this labeling supplement.

### IX. Use in Special Populations

#### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The Sponsor did not provide a gender effects analysis in the original submission. The Sponsor was asked to provide this analysis for the primary efficacy endpoint (requested 8/18/03) and they provided the data on 9/12/03.

The analysis provided by the Sponsor was a pooled analysis for studies 99001 and 99003. The change in MADRS total score from baseline was similar among males and females. The Sponsor did not provide separate statistical analysis results for each gender group, only summary results as in the tables below. Per the Sponsor, there was no statistically significant sex effect or sex by treatment interaction.

Table IX.A.1. Sponsor's Gender Analysis (LOCF): MADRS Total Score Adjusted Mean Change from Baseline [Studies 99001 + 99003] (mean values are rounded)

	Placebo (n = 258)		Escitalopram (n = 254)	
	Mean	SD	Mean	SD
<b><i>Females</i></b>				
Baseline	29	3.8	29	4.1
Week 8	17	9.3	14	8.5
Change from Baseline	-12	9.4	-15	8.4

	Placebo (n = 85)		Escitalopram (n = 89)	
	Mean	SD	Mean	SD
<b><i>Males</i></b>				
Baseline	28	3.7	29	4.8
Week 8	16	9.8	14	9.3
Change from Baseline	-12	9.7	-14	8.8

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The Division also performed a gender analysis (see Statistical Review). This analysis was performed on each individual study whereas the Sponsor's analysis was performed on a pooled analysis (the following tables are from the Statistical Review, tables 4.1 and 4.2). Though the overall difference in MADRS total score from baseline appears similar between males and females per the Sponsor's summary table, the analysis by the Division was unable to detect a difference among male subjects in the analysis of the individual studies. Therefore, it would appear that the majority of the efficacy signal comes from the female subgroup which comprised 75% of enrolled subjects.

Table IX.A.2. Division's Analysis - Study 99001: Subgroup Analysis for Gender on the MADRS Total Score

Variable	Visit	Least Square Means	SE	P-value
<i>Males</i>				
PBO (n=42)	Last (LOCF)	-14.57	1.40	
ESC (n=50)	Last (LOCF)	-15.44	1.46	
ESC-PBO	Last (LOCF)	-0.87	1.79	0.6282
<i>Females</i>				
PBO (n=147)	Last (LOCF)	-13.34	0.81	
ESC (n=138)	Last (LOCF)	-16.36	0.82	
ESC-PBO	Last (LOCF)	-3.02	0.99	0.0025

Table IX.A.3. Division's Analysis - Study 99003: Subgroup Analysis for Gender on the MADRS Total Score

Variable	Visit	Least Square Means	SE	P-value
<i>Males</i>				
PBO (n=43)	Last (LOCF)	-11.04	1.63	
CIT (n=49)	Last (LOCF)	-13.39	1.47	
ESC (n=39)	Last (LOCF)	-14.45	1.70	
CIT-PBO	Last (LOCF)	-2.345	2.24	0.2975
ESC-PBO	Last (LOCF)	-3.41	2.36	<b>0.1524</b>
<i>Females</i>				
PBO (n=111)	Last (LOCF)	-12.05	0.81	
CIT (n=110)	Last (LOCF)	-14.21	0.82	
ESC (n=116)	Last (LOCF)	-15.61	0.79	
CIT-PBO	Last (LOCF)	-2.16	1.13	0.057
ESC-PBO	Last (LOCF)	-3.56	1.11	<b>0.001</b>

#### **B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

The Sponsor did not provide an age, race or ethnicity effects analysis in the original submission. The Sponsor was asked to provide this analysis for the primary efficacy endpoint (requested 8/18/03) and they provided the data on 9/12/03.

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The analysis provided by the Sponsor was a pooled analysis for studies 99001 and 99003. The change in MADRS total score from baseline was similar among subjects < 60 and ≥ 60 years of age, though the number of subjects ≥ 60 years of age was very small. The Sponsor did not provide separate statistical analysis results for each age group, only summary results as in the tables below. Per the Sponsor's analysis, there was no statistically significant treatment by age interaction. The studies did not include many subjects > 60 years of age (~5%), so the conclusions of these findings are limited.

Table IX.B.1. Age Analysis (LOCF): MADRS Total Score Adjusted Mean Change from Baseline [Studies 99001 + 99003] (mean values are rounded)

	Placebo (n = 327)		Escitalopram (n = 326)	
	Mean	SD	Mean	SD
<i>Age &lt; 60</i>				
Baseline	29	3.8	29	4.2
Week 8	16	9.4	14	8.7
Change from Baseline	-12	9.5	-15	8.5

	Placebo (n = 16)		Escitalopram (n = 17)	
	Mean	SD	Mean	SD
<i>Age ≥ 60</i>				
Baseline	30	3.8	29	4.1
Week 8	20	9.4	15	9.0
Change from Baseline	-10	9.2	-13	8.1

The Division also performed an age analysis (see Statistical Review) but used a different age cut-off for the two categories (≤ 50, > 50 years of age). This analysis was performed on each individual study whereas the Sponsor's analysis was performed on a pooled analysis (the following tables are from the Statistical Review, tables 4.3 and 4.4). As with the males in the gender analysis, this analysis was unable to detect a difference for subjects > 50 years of age.

Table IX.B.2. Division's Analysis – Study 99001. Subgroup Analysis for Age on the MADRS Total Scores

Variable	Visit	Least Square Means	SE	P-value
<i>Age = 50</i>				
PBO (n=146)	Last (LOCF)	-13.90	0.83	
ESC (n=148)	Last (LOCF)	-16.69	0.80	
ESC-PBO	Last (LOCF)	-2.79	0.97	0.005
<i>Age &gt; 50</i>				
PBO (n=43)	Last (LOCF)	-12.23	1.58	
ESC (n=40)	Last (LOCF)	-14.84	1.81	
ESC-PBO	Last (LOCF)	-2.61	2.23	0.2481

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Table IX.B.3. Division's Analysis – Study 99003. Subgroup Analysis for Age on the MADRS Total Scores

Variable	Visit	Least Square Means	SE	P-value
<i>Age = 50</i>				
PBO (n=106)	Last (LOCF)	-11.80	0.86	
CIT (n=107)	Last (LOCF)	-13.26	0.86	
ESC (n=111)	Last (LOCF)	-15.60	0.83	
CIT-PBO	Last (LOCF)	-1.47	1.13	0.207
ESC-PBO	Last (LOCF)	-3.81	1.11	<b>0.001</b>
<i>Age &gt;50</i>				
PBO (n=48)	Last (LOCF)	-13.57	1.24	
CIT (n=52)	Last (LOCF)	-13.68	1.22	
ESC (n=44)	Last (LOCF)	-12.41	1.27	
CIT-PBO	Last (LOCF)	-0.11	1.72	0.951
ESC-PBO	Last (LOCF)	1.17	1.76	<b>0.508</b>

Since only 1.2% (8/686) of subjects included in studies 99001 and 99003 were non-Caucasian, the Sponsor did not provide a subgroup analysis by race/ethnicity. The Division also did not perform this analysis due to the small number of non-Caucasian subjects.

#### C. Evaluation of Pediatric Program

NA – Labeling Supplement.

### X. Labeling Issues

Several recommendations for changes in the Sponsor's proposed labeling have been proposed. The most significant of these was deletion of efficacy comments relating to the CGI-S and CGI-I in the Clinical Efficacy Trials section of labeling as these were secondary efficacy measures. The Sponsor has also been asked to include postmarketing data for escitalopram in labeling, currently only postmarketing adverse events for racemic citalopram are included in labeling.

In addition, SSRI class labeling has recently been finalized for discontinuation symptoms, pregnancy/nonteratogenic effects (neonatal withdrawal) and abnormal bleeding – these sections have also been incorporated into the Sponsor's proposed labeling.

### XI. Conclusions and Recommendations

#### A. Conclusions

The Sponsor submitted data from two clinical trials to support changes in the Clinical Efficacy Trials section of labeling. Both clinical trials were 8-week studies in outpatients with major depressive disorder. Study 99001 was a fixed-dose study that included escitalopram 10 mg (n = 188) and placebo (n = 189).

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Study 99003 was a flexible-dose study that included escitalopram 10 – 20 mg (n = 155), citalopram 20 – 40 mg (n = 159) and placebo (n = 154). Neither of these clinical trials involved U.S. sites.

The two clinical trials submitted support the efficacy of escitalopram 10 to 20 mg/day in the treatment of major depressive disorder. The primary efficacy endpoint was the change in MADRS total score (8 weeks compared to baseline) comparing escitalopram to placebo. The LOCF analysis for both trials showed statistical significance in favor of escitalopram (p = 0.002 for both Studies 99001 and 99003); the OC findings were similar. The overall mean difference between escitalopram and placebo on the MADRS was 2.7 to 2.9 points.

In this submission, the Sponsor also included a study (SCT-MD-10) evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests. Proposed changes in labeling are supported by the findings from this study.

Safety data from studies 99001 and 99003 were included in the original NDA ISS submitted on 3/23/01 and were reviewed at that time (Medical Officer: K. Brugge, MD). The only additional safety data in the current submission was that submitted for protocol SCT-MD-10, a study evaluating the effects of escitalopram and the combination escitalopram + alcohol versus placebo and alcohol on various cognitive and psychomotor tests in healthy volunteers. No deaths or serious adverse events occurred in this small study (n = 16). Adverse events that occurred in this trial are described in current labeling.

#### **B. Recommendations**

I recommend that the Division take an approvable action for supplemental NDA 21-323/SE8-007. In this labeling supplement, the Sponsor has submitted data from two clinical trials to add to the Clinical Efficacy Trials section of labeling and proposes to delete reference to racemic citalopram in this section of labeling. The data regarding the efficacy of Lexapro in the treatment of major depressive disorder, for which this SSRI already has an indication, is supported by the submitted clinical trials.

Cara Alfaro, Pharm.D.  
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FDA CDER ODE1 DNDP HFD-120  
October 31, 2003

cc: Laughren/Andreason/David/Chen

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### Appendix

Table C-1.1-A. List of Sites for Study 99001

	# Pts Randomized	# Pts Completed		# Pts Randomized	# Pts Completed
<b>Canada</b>			<b>France (cont.)</b>		
#1001 S. Kutcher	18	12	#1121 F. Lacoïn	7	5
#1010 S. Kutcher	24	18	#1122 B. Daubin	3	2
#1020 S. Kutcher	14	14	#1123 M. Pithon	4	4
			#1124 G. Binet	12	12
<b>France</b>			#1125 H. Vilarem	12	12
#1101 A. Chaleon	4	4	#1126 JM Lerouge	4	3
#1102 D. Sacareau	8	6	#1127 JY Vogel	8	8
#1103 F. Grivet	3	2			
#1104 O. Perez	3	2	<b>United Kingdom</b>		
#1105 P. Marmor	8	7	#1201 A. Wade	73	48
#1106 C. Lousqui	11	11			
#1107 J.R. Auriault	4	4	<b>The Netherlands</b>		
#1108 J.L. Gabrielli	4	4	#1302 NF Vogel	2	1
#1109 P. Dumond	7	7	#1304 P de Graaf	4	4
#1110 M. Bismuth	8	7	#1312 T. Ehling	3	1
#1111 M Bouet	8	7	#1313 D. Schnipper	3	3
#1112 C. Fabié	4	3	#1314 D. Schnipper	1	0
#1113 C. Fivel	3	3			
#1114 P. Fuchs	4	4	<b>Estonia</b>		
#1115 B. Gay	2	2	#2001 S. Vään	16	14
#1116 G. Rouviere	8	6	#2002 A. Sild	16	15
#1117 O. Decloux	8	7	#2003 A. Puusild	19	19
#1118 L. Goepfert	4	4	#2004 K. Jaanson	24	24
#1119 J.L. Huberschwiller	8	7			
#1120 J.C. Haus	4	4			

#### C-1.3-A Exclusion Criteria

1. Female subjects of childbearing potential: pregnant or breast-feeding, without adequate contraception (oral contraception, systemic contraception, surgical sterilization, IUD or diaphragm in conjunction with spermicidal foam and condom on male partner), positive pregnancy test at screening.
2. Patients who currently meet the DSM-IV criteria for Mania or any Bipolar Disorder, Schizophrenia or any psychotic disorder, Obsessive-Compulsive Disorder, current eating disorders, Mental Retardation, any Pervasive Developmental Disorder or Cognitive Disorder.
3. Alcohol or drug abuse as defined in the DSM IV within the previous 12 months.
4. In the investigator's opinion the patient has a significant risk of suicide and/or  $\geq 5$  points on item 10 of the MADRS scale.
5. Use of disallowed therapy:
  - Oral antipsychotic drugs within 2 weeks and depot preparations within 6 months prior to screening
  - MAOIs within the last 2 weeks prior to screening

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- Hypnotics and anxiolytics (except for benzodiazepines used for insomnia in a stabilized dose during the last 6 months or used episodically in the lower part of the recommended dose range)
  - Barbiturates, chloral hydrate
  - Fluoxetine within the last 5 weeks prior to screening and other SSRIs and TCAs within the last 2 weeks prior to screening
  - SNRI within the last one week prior to screening (except or mirtazapine: within the last 2 weeks prior to screening)
  - Ongoing prophylactic treatment with lithium, valproate sodium or carbamazepine
  - Treatment with ECT within the last 6 months
6. Patients who are currently receiving formal behavior therapy or systematic psychotherapy or plan to initiate such therapy during the trial
  7. Lack of response to previous treatment with citalopram (including current episode)
  8. Treatment with an investigational drug within 30 days prior to study entry
  9. Known hypersensitivity to citalopram
  10. History of severe drug allergy or hypersensitivity
  11. Laboratory values outside normal ranges, considered by the investigator to be of clinical significance
  12. Diseases which could, judged by the investigator, interfere with the assessments of safety, tolerability and efficacy
  13. Serious illness and/or serious sequelae of: liver or renal insufficiency, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological (epilepsy included), infectious, neoplastic or metabolic disturbance
  14. The patient is, in the opinion of the investigator, unlikely to be able to comply with the clinical trial protocol or is unsuitable for any other reason

#### Table C-1.6-A. Secondary Efficacy Endpoints

- MADRS total score at each visit
- Proportion of patients with  $\geq 50\%$  reduction in MADRS total score from baseline
- Proportion of patients with MADRS total score  $\leq 12$  per visit
- CGI-S score per visit and at week 8
- Change from baseline to each visit of CGI-S score and at week 8
- Proportion of patients with a CGI-S score  $\leq 2$  per visit
- CGI-I score per visit and at week 8
- Proportion of patients with a CGI-I score  $\leq 2$  per visit and at week 8
- Change from baseline to final assessment of MADRS single items

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Table C-1.9-A Concomitant Medications: Study 99001

Placebo Group

Subject	Concomitant Med	Duration of use (days)	Started on Study Day	Duration of Concomitant Use (Days)
0218	Lorazepam 0.5 prn	NA	50	Unknown
0223	Hypericum #3 caps	NA	NA	Unknown
0219	Zopiclone 7.5 prn	NA	NA	Unknown
0226	Temazepam 15 mg prn	46	-16	30
0164	Zolpidem #1/day prn	5	32	5
0169	Prazepam 10 mg prn	11	-10	1
0381	Fluoxetine 20 mg	NA	NA	Unknown
0346	Hypericum extract #100 gtts/day	NA	-182	Unknown
0034	Prazepam 30 mg	NA	NA	Unknown
0359	Alprazolam 4 mg	NA	-20	Unknown
0360	Buspirone 20 mg	14	-13	1
0093	Zopiclone 7.5 mg	1673	-1672	1
	Alprazolam 0.125 mg	NA	-1406	Unknown
	Zopiclone 3.75 mg	1	32	1
0037	Valerian #6/day	28	-27	1
0038	Valerian #6/day	12	-11	1
	Zopiclone 3.75 mg	12	-11	1
0178	Bromazepam 3 mg	NA	32	Unknown
0103	Bromazepam 3 mg	NA	-231	Unknown
0124	Clonazepam 1 mg prn	NA	-719	Unknown
0182	Clonazepam 1.5 mg	NA	-93	Unknown
0003	Temazepam 20 mg	NA	-1943	Unknown
0020	Lormetazepam 1 mg	NA	-238	Unknown
0152	Amitriptyline 100 mg	NA	30	Unknown
0198	Fluoxetine 20 mg	NA	33	Unknown
0291	Temazepam 20 mg	8	-6	2
0302	Hypericum 40 mg	36	-34	2
0307	Temazepam 10 mg prn	NA	-145	Unknown
0325	Oxazepam 10 mg	NA	NA	Unknown
	Clonazepam 0.5 mg prn	NA	NA	Unknown
	Mirtazapine 30 mg	NA	NA	Unknown
0310	Zopiclone 7.5 mg	14, 19	17, 43	33
	Diazepam 5 mg	15	17	15
	Diazepam 5 mg	18	44	18
0412	Alprazolam 0.75 mg	57	-46	11
	Alprazolam 0.5 mg	6	11	6
	Alprazolam 0.375 mg	14	17	14
	Alprazolam 0.25 mg	34	31	34
	Valerian 90 mg	NA	35	Unknown
0261	Phenazepam 1 mg	NA	-5	Unknown
0265	Bromazepam 3 mg	23	29	23
	Lorazepam 1 mg	NA	52	Unknown
0267	Nitrazepam 5 mg	14	-5	9
	Nitrazepam 5 mg	8	22	8
0313	Diazepam 5 mg	94	-24	70
0415	Diazepam 5 mg	49	1	49
	Diazepam 10 mg	14	50	14
0276	Diazepam 5 mg	7	-6	1
0324	Clonazepam 1 mg	19, 1	-4, 50	16

NA = not available

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### Escitalopram Group

Subject	Concomitant Med	Duration of use (days)	Started on Study Day	Duration of Concomitant Use (Days)
0217	Alprazolam 0.5 prn	12	-6	6
0238	Lorazepam 1 mg prn 2-3x/week	22, 7	15, 37	29
0431	Lorazepam 1 mg prn 2x/week	NA	22	Unknown
0162	Buspirone 0 - 30 mg	15	-14	1
0117	Lorazepam 1 mg	NA	-208	Unknown
0250	Lorazepam 0.25 mg prn	NA	-1139	Unknown
0165	Valerian #2/day	32	-31	1
	Zolpidem 20 mg	32	-31	1
0172	Bromazepam 6 mg	NA	NA	Unknown
0383	Valproic acid #2	21	-20	1
0073	Valerian #4/day	29	-27	2
0176	Venlafaxine 25 mg	NA	71	Unknown
	Nordazepam 15 mg	NA	71	Unknown
	Zopiclone 7.5 mg	NA	71	Unknown
	Valpromide 600 mg	NA	71	Unknown
0094	Nordazepam 3.75 mg	15	0	15
	Tetrazepam 25 mg	8	14	8
0095	Clonazepam 1 mg	NA	NA	Unknown
0079	Bromazepam 3 mg	NA	NA	Unknown
0039	Bromazepam 3 mg prn	NA	-255	Unknown
0040	Alprazolam 0.125 mg	NA	NA	Unknown
0356	Clorazepate 30 mg	1	57	1
0092	Loprazolam 1 mg	4	-3	1
0041	Lorazepam 1 mg	NA	-206	Unknown
0042	Alprazolam 0.25 mg	1	10	1
0177	Bromazepam 1.5 mg 3x/week	61	-60	1
0180	Sulpiride 150 mg	15	-14	1
	Alprazolam 0.50 mg	9	-8	1
0045	Maprotiline 25 mg	NA	NA	Unknown
	Bromazepam 3 mg	NA	NA	Unknown
0184	Bromazepam 3 mg	NA	-126	Unknown
0058	Alprazolam 0.25 mg	294	-258	36
0194	Zolpidem 5 mg prn	1076	-1074	2
0017	Hypericum 900 mg	NA	NA	Unknown
0144	Paroxetine 20 mg	NA	NA	Unknown
0326	Amitriptyline 75 mg	NA	NA	Unknown
	Ketazolam 15 mg	NA	NA	Unknown
0254	Zopiclone 7.5 mg	NA	NA	Unknown
0260	Oxazepam 20 mg	32	-3	29
	Zopiclone 7.5 mg	17	29	17
0409	Zopiclone 7.5 mg	11	18	11
0264	Diazepam 5 mg	15	10	15
	Diazepam 10 mg	41	24	41
0266	Diazepam 5 mg	3, 4	0, 15	7
0316	Diazepam 5 mg	18	-3	15
0413	Bromazepam 3 mg	48	5	48
	Phenazepam 2 mg	46	-40	6
	Bromazepam 6 mg	15	53	15
0272	Diazepam 5 mg	4	-3	1
0274	Diazepam 20 mg	1	12	1
0336	Diazepam 5 mg	1	20	1
0323	Alprazolam 1 mg	80	-78	2
	Clonazepam 2 mg	38	-8	30

NA = not available

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Table C-1.10.1.1-A. Study 99001: Results from Selected Secondary Efficacy Endpoints (LOCF) – Week 8 Data Shown

	Placebo (n = 189)	Escitalopram (n = 188)	Difference (95% CI) p-value
Proportion of Subjects with $\geq$ 50% Reduction in MADRS Total Score	42% (79/189)	55% (104/188)	13.5 (3.5, 23.5) p = 0.010
Proportion of Subjects with MADRS Total Score $\leq$ 12	34% (64/189)	47% (89/188)	13.5 (3.7, 23.3) p = 0.009
CGI-S	2.97	2.74	-0.23 (-0.46, 0) p = 0.054
CGI-I	2.39	2.06	-0.33 (-0.56, -0.09) p = 0.006

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Table C-2.1-A. List of Sites for Study 99003

	# Pts Randomized	# Pts Completed
<b>Canada</b>	69	
#1001 A.V. Ravindran	2	1
#1002 R.T. Reesal	12	10
#1003 P. Latimer	9	9
<b>France</b>		
#1102 C. Aliotti	6	6
#1104 G. Cèbe	6	6
#1106 P. Darné	1	1
#1107 F. Dejean	12	12
#1109 A. Delachienne	6	6
#1110 P.G. Diss	3	3
#1111 B. Ducournau	6	5
#1112 G. Duroux	5	5
#1114 G. Forcada	11	11
#1115 C. Francois	3	3
#1116 L. Herlet	6	6
#1117 D. Herman	6	6
#1120 P. Jehl	5	5
#1121 J. M. Larrode	6	6
#1122 M. Maurel	6	6
#1124 G. Mongin	6	6
#1126 J.L. Navarre	6	4
#1127 D. Parent	5	5
#1128 J.P. Peynaud	4	4
#1130 V. Ratsianoharana	5	4
#1131 P. Sauveur	6	6
#1133 M. Vignes	2	2
<b>United Kingdom</b>		
#1201 A. Smithers	6	5
#1202 P. Harvey	6	6
#1203 R. Pool	4	4
#1205 A.H. Jones	12	11
#1206 A. Cowie	6	5
#1207 P.J. Davies	5	3
#1208 M. Adler	12	12
#1209 J. Simmons	6	6
#1210 T. Gooding	18	18
#1211 A. Weaver	6	6
#1212 R.L. Sarin	6	5
#1213 S. Butt	5	3

	# Pts Randomized	# Pts Completed
<b>United Kingdom (cont.)</b>		
#1214 D.S. Fernando	10	9
#1215 T. Cahill	12	11
#1216 B. Bodalia	15	14
#1217 R. Rolls	6	3
#1218 R. Cranfield	6	6
<b>Belgium</b>		
#1401 F. Vandebuërie	6	6
#1402 P. Van Langenhove	6	6
#1404 G. Mehuys	5	5
<b>Finland</b>		
#1501 U. Lepola	18	18
#1503 P. Tamminen	4	4
#1504 J. Penttinen	18	15
#1505 T. Alapieti	12	12
#1506 R. Kerätär	2	2
#1507 K. Pakkala	6	6
#1509 R. Tanskanen	12	12
#1510 M. Vanhala	8	6
#1512 J. Teirilä	6	6
#1513 H. Koponen	9	9
<b>Switzerland</b>		
#1601 U. Meinecke	1	1
#1605 B. Blajev	12	12
#1608 R. Vogt	4	3
#1701 R. Adolfsson	11	9
#1704 G. Lif	1	1
#1801 R. Rabe	6	6
#1802 M. Bastøe	2	2
#1805 M. Mundal	7	5
#1806 T. Hatlebrette	10	10
#1807 K. Olsen	2	2
#1808 H.J. Helgesen	4	4
#1809 T. Eikeland	11	8
#1810 B. Spies	2	2

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Table C-2.9-A Concomitant Medications: Study 99003

Placebo Group

Subject	Concomitant Med	Duration of use (days)	Started on Study Day	Duration of Concomitant Use (Days)
2554	Amfebutamone 300 mg	NA	NA	Unknown
3558	Amitriptyline 150 mg	NA	NA	Unknown
3076	Alprazolam 3 mg	114	-113	1
	Flunitrazepam 1 mg	215	-214	1
3128	Alprazolam 2 mg	NA	-21	Unknown
3129	Clorazepate 10 mg	17	-16	1
3145	Bromazepam 1.5 mg	NA	-143	Unknown
3215	Alprazolam 0.25 – 0.50 mg	NA	-2751	Unknown
3086	Zolpidem 10 mg	NA	NA	Unknown
3501	Paroxetine 20 mg	NA	16	Unknown
3410	Citalopram 20 mg	NA	59	Unknown
3090	Lormetazepam 1 mg	110	-48	62
3229	Lorazepam 10 mg	NA	NA	Unknown
3084	Clorazepate 15 mg	4	-2	2
3173	Prazepam 10 mg	NA	-637	Unknown
3175	Mianserin #1.5	NA	-107	Unknown
	Lorazepam #1	NA	-48	Unknown
	Alimemazine #50 gtts	NA	-107	Unknown
	Alimemazine #10 gtts	NA	NA	Unknown
	Lormetazepam #1/2	NA	-90	Unknown
3177	Lormetazepam #1	NA	-796	Unknown
	Lormetazepam #1/2	NA	NA	Unknown
3264	Reboxetine 8 mg	NA	54	Unknown
3398	Zopiclone 7.5 mg prn	NA	-41	Unknown
3343	Citalopram 20 mg	NA	63	Unknown
3279	Citalopram 20 mg	29	63	29
	Fluoxetine 20 mg	NA	92	Unknown
3434	Fluoxetine 20 mg	NA	65	Unknown
3457	Citalopram 20 mg	NA	63	Unknown
3349	Temazepam 10 – 20 mg	NA	11	Unknown
	Fluoxetine 20 – 40 mg	NA	11	Unknown
1401	Clorazepate prn	NA	NA	Unknown
3032	Temazepam 10 mg	5	29	5
	Temazepam 10 mg	NA	36	Unknown
3182	Diazepam 5 mg	NA	NA	Unknown
3293	Temazepam 10 mg	NA	NA	Unknown
3374	Citalopram 20 mg	NA	13	Unknown
3581	Mianserin 30 mg	NA	NA	Unknown
3053	Alprazolam 0.25 – 0.5 mg prn	NA	NA	Unknown
	Temazepam 20 mg	NA	32	Unknown
3046	Alprazolam #3/month	NA	NA	Unknown
	Diazepam 5 – 10 mg prn	NA	17	Unknown
3447	Temazepam 20 mg	NA	0	Unknown
3244	Oxazepam 15 mg	22	-20	2
3439	Temazepam #1	NA	1	Unknown
	Zopiclone 7.5 – 15 mg	9	-8	1
3059	Diazepam 2 mg	NA	NA	Unknown
	Diazepam 2 mg	1	13	1
	Diazepam 5 mg	12	52	12
	Diazepam 2.5 mg	4	64	4
3518	Lorazepam 0.5 mg	NA	NA	Unknown

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### Placebo Group (cont.)

Subject	Concomitant Med	Duration of use (days)	Started on Study Day	Duration of Concomitant Use (Days)
3520	Clorazepate 10 mg	NA	-238	Unknown
3603	Clorazepate 5 mg	NA	-773	Unknown
3027	Zopiclone 5 mg	NA	-1	Unknown
3002	Zopiclone 7.5 mg	51	-14	37
	Oxazepam 15 mg	NA	36	
3508	Oxazepam 12.5 mg prn	NA	-7	Unknown
3110	Zopiclone 1-2/week	NA	NA	Unknown
3119	Citalopram 20 – 30 mg	NA	NA	Unknown

### Citalopram Group

Subject	Concomitant Med	Duration of use (days)	Started on Study Day	Duration of Concomitant Use (Days)
3494	Lorazepam 2 mg	NA	NA	Unknown
3206	Bromazepam 3 mg	NA	NA	Unknown
3077	Zolpidem 10 mg	10	-9	1
	Alprazolam 0.25 mg	10	-9	1
	Tetrazepam 50 mg	10	0	10
3121	Prazepam 10 mg	NA	-387	Unknown
3127	Clobazam 10 mg	NA	NA	Unknown
	Clobazam 5 mg	NA	NA	Unknown
3098	Tetrazepam 50 mg	30	-1	29
3163	Vagostabyl #6/day	6	-5	1
3132	Sertraline 50 mg	NA	NA	Unknown
3147	Lorazepam 2.5 mg	NA	NA	Unknown
	Tianeptine 37.5 mg	NA	15	Unknown
3149	Alprazolam 0.25 mg	NA	-682	Unknown
3164	Vagostabyl #6/day	13	-11	2
3089	Lormetazepam 1 mg	NA	-96	Unknown
3079	Valerian 100 – 120 mg	5	38	5
3169	Lorazepam 1 mg	24	-23	1
3179	Bromazepam #1/2	NA	NA	Unknown
3180	Lormetazepam 1 mg	NA	NA	Unknown
3545	Diazepam 5 mg prn	NA	-1702	Unknown
3337	Citalopram 20 mg	NA	65	Unknown
3276	Zopiclone #2 prn	223	-182	41
	Citalopram 20 mg	NA	36	Unknown
3344	Citalopram 20 mg	NA	64	Unknown
3278	Paroxetine 20 mg	NA	-61	Unknown
	Citalopram 20 mg	NA	78	Unknown
3538	Temazepam 10 mg	NA	NA	Unknown
3539	Citalopram 20 mg	NA	65	Unknown
3409	Diazepam 6 – 12 mg prn	NA	10	Unknown
3413	Diazepam 2 mg prn	NA	-98	Unknown
	Lormetazepam 0.5 mg prn	NA	-98	Unknown
3307	Loprazolam 1 mg	159	-157	2
3415	Citalopram 20 mg	NA	65	Unknown
3255	Venlafaxine 75 mg	NA	NA	Unknown
3323	Bromazepam 3 mg	NA	-3878	Unknown
3033	Oxazepam 30 mg prn	NA	NA	Unknown
3294	Temazepam 10 mg	NA	NA	Unknown

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### Citalopram Group (cont.)

Subject	Concomitant Med	Duration of use (days)	Started on Study Day	Duration of Concomitant Use (Days)
3191	Zopiclone 7.5 mg	1, 1, 1, 1, 1, 1, 2, 1, 1, 1, 3, 3, 3, 2, 2, 1, 1	5, 8, 10, 19, 20, 21, 23, 27, 32, 36, 38, 41, 47, 52, 57, 64, 66	26
3192	Temazepam 20 mg Temazepam #1/2	1, 1, 4, 4, 4, 3, 1 1, 1, 1, 3	10, 14, 41, 48, 55, 62, 69 27, 30, 32, 36	24
3194	Zopiclone #1 prn	NA	52	Unknown
3052	Zopiclone 7.5 mg	NA	NA	Unknown
3045	Zopiclone 3.75 – 7.5 mg Zolpidem 5 – 10 mg Temazepam 10 – 20 mg	NA NA NA	NA NA -2	Unknown Unknown Unknown
3448	Temazepam 10 – 20 mg	NA	NA	Unknown
3245	Temazepam 20 mg	NA	-28	Unknown
3456	Temazepam 30 – 40 mg	NA	-261	Unknown
3522	Lorazepam 0.5 mg	NA	-211	Unknown
3466	Hypericum 600 mg Valerian 500 mg	NA NA	NA NA	Unknown Unknown
3026	Zopiclone 5 mg	NA	NA	Unknown
3007	Citalopram 30 mg	NA	0	Unknown
3111	Zopiclone 7.5 mg Diazepam 5 mg	7, NA 2	1, 10 8	Unknown 2
3116	Nitrazepam 5 mg prn	NA	-92	Unknown
3019	Zopiclone 7.5 mg Alimemazine 10 mg	1 1	6 8	1 1

### Escitalopram Group

Subject	Concomitant Med	Duration of use (days)	Started on Study Day	Duration of Concomitant Use (Days)
3210	Nordazepam 7.5 mg	NA	-3787	Unknown
3130	Fluoxetine 10 mg	32	-54	22 day washout
3131	Diazepam 5 mg	NA	NA	Unknown
3097	Tetrazepam 50 mg	2	29	2
3379	Sertraline 50 mg	NA	-248	Unknown
3150	Prazepam 10 mg	NA	-392	Unknown
3211	Lorazepam 1 mg Noctran 10 10 mg	NA NA	-7016 -7016	Unknown Unknown
3166	Vagostabyl #6/day	3	-2	1
3085	Zolpidem 10 mg Zolpidem 5 mg	600 NA	-580 20	20 Unknown
3088	Lormetazepam 1 mg	NA	25	Unknown
3176	Bromazepam #1/2	NA	NA	Unknown
3178	Nordazepam #1/2	956	-905	51
3259	Citalopram 20 mg	NA	66	Unknown
3546	Chlordiazepoxide 30 mg	NA	16	Unknown
3338	Citalopram 20 mg	NA	67	Unknown
3271	Temazepam 20 mg	NA	-2022	Unknown
3277	Citalopram 20 mg	NA	70	Unknown
3435	Citalopram 20 mg	NA	62	Unknown
3436	Citalopram 20 mg Fluoxetine 20 mg	29 NA	72 101	29 Unknown

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### Escitalopram Group (cont.)

Subject	Concomitant Med	Duration of use (days)	Started on Study Day	Duration of Concomitant Use (Days)
3355	Citalopram 20 mg	13	64	13
	Citalopram 40 mg	NA	77	Unknown
3360	Hypericum 900 – 1000 mg	NA	63	Unknown
3462	Zopiclone 7.5 mg	1, 1, 1	16, 18, 47	3
3035	Sertraline 50 mg	NA	NA	Unknown
	Oxazepam 15 mg 3x/week	4	14	4
	Temazepam 20 mg 3x/week	26	11	26
	Alprazolam 0.5 mg 4x/week	8	22	8
	Temazepam 10 mg 5x/week	NA	37	Unknown
3284	Clonazepam 0.5 mg 2x/week	NA	NA	Unknown
3181	Diazepam 5 mg	1, 1, 1, 1	3, 8, 11, 14	4
	Temazepam 20 mg	14	15	14
	Temazepam 20 mg	NA	30	Unknown
3183	Temazepam 10 mg	NA	-1	Unknown
3377	Temazepam 20 mg prn	54	-7	47
3187	Temazepam #1 prn	NA	-314	Unknown
3578	Oxazepam #1	NA	-4	Unknown
3043	Zopiclone 3.75 – 7.5 mg	NA	NA	Unknown
	Temazepam 10 mg	1	31	1
3449	Temazepam 10 – 20 mg	NA	14	Unknown
3242	Temazepam 20 mg	NA	47	Unknown
3058	Temazepam 20 mg	11	1	11
	Alprazolam 0.25 mg	1, 2, 5	31, 41, 45	8
3605	Bromazepam 1.5 mg	NA	NA	Unknown
3606	Clobazam 5 mg	NA	NA	Unknown
	Fluoxetine 40 mg	NA	NA	Unknown
	Clobazam 2.5 mg	NA	19	Unknown
4283	Flunitrazepam NA	NA	8	Unknown
4291	Zopiclone 7.5 mg prn	44	-2	42
3025	Flunitrazepam 1 mg	NA	NA	Unknown
	Oxazepam 15 mg	NA	NA	Unknown
3507	Zopiclone prn	628	-564	64

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Table C-2.10.1.1-A Study 99003: Results from Selected Secondary Efficacy Endpoints (LOCF) – Week 8 Data Shown

	Placebo (n = 154)	Citalopram (n = 159)	Escitalopram (n = 155)	Difference (95% CI) p-value
Proportion of Subjects with $\geq$ 50% Reduction in MADRS Total Score	43 (67/154)	50% (79/159)	61% (95/155)	Cit-PC: 6.2 (-4.9, 17.2) p = 0.308 Esc-PC: 17.8 (6.8, 28.7) p = 0.002
Proportion of Subjects with MADRS Total Score $\leq$ 12	41% (63/154)	40% (63/159)	50% (78/155)	Cit-PC: -1.3 (-12.2, 9.6) p = 0.819 Esc-PC: 9.4 (-1.6, 20.5) p = 0.110
CGI-S	2.80	2.67	2.48	Cit-PC: -0.15 (-0.40, 0.10) p = 0.245 Esc-PC: -0.38 (-0.64, -0.13) p = 0.003
CGI-I	2.48	2.17	2.08	Cit-PC: -0.31 (-0.55, -0.06) p = 0.014 Esc-PC: -0.43 (-0.67, -0.18) p = 0.001

Table C-3.3-A. Study SCT-MD-10 Exclusion Criteria

- Subjects with concurrent diseases that might interfere with the conduct of the study, confound interpretation of the study results, or endanger the subject's well-being. Subjects with evidence or history of malignancy (other than excised basal-cell carcinoma) or any significant hematological, endocrine, cardiovascular, respiratory, renal, hepatic, immunologic, gastrointestinal, psychiatric or neurologic disease. If there was a history of such disease but the condition had been stable for > 1 year and was judged by the Investigator not to interfere with the subject's participation in the study, the subject could be included, with the documented approval of the Medical Monitor.
- Female subjects who were pregnant or breastfeeding
- Subjects who had consumed alcohol within 72 hours prior to screening
- Subjects who had used any prohibited medications within 2 weeks prior to baseline
- Subjects who tested positive on the urine drug screen for prohibited drugs, drugs of abuse or alcohol at screening or baseline
- Subjects who had a history of drug or alcohol abuse within the last 5 years
- Subjects who had a history of hypersensitivity reactions to citalopram or alcohol
- Subjects who had, at screening or baseline, a sitting systolic BP > 180 mmHg or < 100 mm Hg; a sitting diastolic BP of > 100 mm Hg or < 60 mm Hg; or a pulse rate > 100 bpm or < 50 bpm
- Subjects who were unable to complete the practice or baseline psychomotor performance test battery
- Subjects who had a Weschsler Adult Intelligence Scale (WAIS) vocabulary raw score < 32 at screening
- Subjects who participated in any other clinical investigation using an experimental drug within 30 days of the start of the study
- Subjects who had previously participated in an investigational study of escitalopram
- Subjects who were employees or relatives of employees of the investigational site
- Subjects who, in the judgement of the investigator, were unlikely to follow the study protocol or are otherwise unsuitable for the study

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/s/

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Cara Alfaro  
11/3/03 08:15:42 AM  
PHARMACIST

Thomas Laughren  
11/12/03 12:28:43 PM  
MEDICAL OFFICER  
I agree that this supplement is approvable.--TPL

## Review and Evaluation of Clinical Data

NDA # 21-323 SE8-007

Sponsor: Forest Laboratories

Drug: Escitalopram (Lexapro)

Drug category: Antidepressant

Material submitted: Response to Approvable Letter – Labeling Negotiations

Indication: Treatment of Major Depressive Disorder

Correspondence date: 12/4/03

Date Review Completed: 12/15/03

### **Background**

The supplemental NDA for escitalopram for the inclusion of additional clinical trials data in labeling for the treatment of Major Depressive Disorder was submitted to the Division on 2/6/03. An approvable letter was issued on 11/25/03, the letter outlined several changes in the proposed labeling previously submitted by the Sponsor. The Sponsor submitted a revised version of labeling on 12/4/03 and a teleconference was held between the Sponsor and the Division on 12/11/03 to discuss the revised labeling. This review briefly outlines the labeling changes requested by the Division.

### **Revisions to Labeling**

#### Generalized Anxiety Disorder

Revisions to labeling that pertain to the Generalized Anxiety Disorder indication have been previously reviewed (K. Brugge, Medical Officer).

#### Class Labeling

Several sections were added to labeling that reflect recent SSRI class labeling actions.

- Discontinuation of Treatment with Lexapro (discontinuation/withdrawal symptoms) in Precautions
- Abnormal Bleeding in Precautions, Information for Patients and Drug Interactions sections of labeling
- Pregnancy – Nonteratogenic Effects (neonatal complications of maternal use of SSRIs) in Precautions and Dosage and Administration sections of labeling

#### Labeling Specific to Lexapro/MDD Supplement

The most significant proposed changes to labeling with regard to Lexapro occurring during review of the Major Depressive Disorder supplement were:

- Deletion of secondary endpoints described in the Clinical Trials section of labeling
- Inclusion of postmarketing adverse events specific to Lexapro

The Sponsor has a section in labeling entitled “Events Reported Subsequent to the Marketing of Racemic Citalopram”, however, a similar section for postmarketing data for Lexapro was not

included in their proposed labeling. In the approvable letter, the Division asked for inclusion of postmarketing adverse events specifically for Lexapro. The Sponsor submitted this data in a separate section of labeling, however, some of the adverse events were not specific for Lexapro since they were also listed in the section for postmarketing adverse events occurring for Celexa. Additionally, no data was submitted to verify the accuracy of the list of adverse events included in this revised labeling.

### **Conclusions and Recommendations**

In response to the approvable letter issued on 11/25/03, the Sponsor submitted revised labeling for this supplemental NDA on 12/4/03. General agreement on the proposed labeling was reached between the Sponsor and Division via a teleconference held on 12/11/03. The only section of labeling that cannot be adequately reviewed at this time is the addition of the postmarketing adverse events specific to Lexapro, a section added in response to the Division's approvable letter. The Division could take an approval action with regard to the other labeling changes and the Sponsor could submit a labeling supplement which specifically addresses this section of labeling. This labeling supplement should include the postmarketing data on which this section of labeling is based as such data was not included with the revised labeling submitted on 12/4/03.

Cara Alfaro, Pharm.D.  
Interdisciplinary Scientist/Pharmacist  
Division of Neuropharmacological Drug Products

December 15, 2003

cc: Laughren/Andreason/David/Alfaro

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/s/

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Cara Alfaro  
12/15/03 08:53:21 PM  
PHARMACIST

Thomas Laughren  
12/16/03 08:18:31 AM  
MEDICAL OFFICER

All labeling issues except for the Postmarketing Reports subsection  
specific to Lexapro have now been resolved, and  
I agree that this can be addressed postapproval;.--TPL

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

**DATE:** November 12, 2003

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approvable Action for  
Escitalopram tablets for the treatment of major depressive disorder (MDD)

**TO:** File NDA 21-323/S-007  
[**Note:** This overview should be filed with the 2-6-03  
original submission.]

**1.0 BACKGROUND**

Escitalopram is a selective serotonin reuptake inhibitor. It is the S-enantiomer of racemic citalopram, which is currently approved and marketed for depression in an immediate release tablet, i.e., Celexa (NDA 20-822, originally approved for depression on 7-17-98). Essentially all of the serotonin reuptake blocking activity of the racemate resides in the S-enantiomer, thus independent development of the S-enantiomer for MDD was a rational undertaking. The proposed dose range for escitalopram in MDD is 10 to 20 mg/day. NDA 21-323 for Lexapro (escitalopram) was approved on 8-14-02.

NDA 21-323 was approved on the basis of a single positive study in MDD, i.e., SCT-MD-01. The NDA had included the results of 4 short-term studies in MDD, however, the statistical data sets for 2 of these studies (99001 and 99003) were not included in the original submission, and the 4<sup>th</sup> study, SCT-MD-02, was considered a failed study. While the statistical data sets were submitted 4 months into the review cycle for studies for studies 99001 and 99003 in this original NDA, this was considered too late to include their review in the original NDA. Since we had already agreed that Lexapro could be approved on the basis of a single study, the NDA was approved, with labeling that indicated that the approval was based in part on the results of study SCT-MD-01 but also on the basis of extrapolation from positive studies for racemic citalopram.

In S-007, the sponsor has submitted the results of studies 99001 and 99003 in support of a change to the labeling that removes references to the fact that the approval was based in part on the basis of extrapolation from positive studies for racemic citalopram and adds references to the approval being based entirely on studies with escitalopram. The sponsor has also submitted the results of

SCT-MD-10, an alcohol interaction study, again in support of changes in labeling that remove references to racemic citalopram.

We did not have any communication with the sponsor with regard to the submission of this supplement, except for our advice in the approval letter for Lexapro that a supplement would be needed to support the labeling changes they sought. The studies supporting this supplement were conducted under IND 58,380, which was originally submitted 5-27-99. This supplement was submitted 2-6-03.

This NDA required no reviews by the CMC, pharmacology/toxicology, or biopharmaceutics groups. The primary review of the efficacy and safety data was done by Cara Alfaro, Ph.D., from the clinical group. Yeh-Fong Chen, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

We decided not to take this NDA to the Psychopharmacological Drugs Advisory Committee.

## **2.0 CHEMISTRY**

As Lexapro is a marketed product, there were no chemistry issues requiring review for this supplement.

## **3.0 PHARMACOLOGY**

As Lexapro is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

## **4.0 BIOPHARMACEUTICS**

As Lexapro is a marketed product, there were no biopharmaceutics issues requiring review for this supplement.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

#### **5.1.1 Overview of Studies Pertinent to Efficacy**

Our review of efficacy was based on the results of 2 double-blind, randomized, 8-week, placebo-controlled, parallel group non-US trials (99001 and 99003) in adult outpatients meeting DSM-IV criteria for major depressive disorder (MDD).

## 5.1.2 Summary of Studies Pertinent to Efficacy Claims

### 5.1.2.1 Study 99001

This was a randomized, double-blind, parallel group, 8-week, fixed-dose multicenter study (40 non-US sites, including Canada, Estonia, France, the Netherlands, and the UK) comparing escitalopram immediate release tablets (10 mg/day, taken as a single am or pm dose), and placebo in adult outpatients meeting DSM-IV criteria for MDD. There were roughly 190 patients per each of the 2 groups in the sample analyzed (n=377), with the % completing to 8 weeks ranging from 84 to 85%. The patients were about 3/4 female, about 98% Caucasian, and the mean age was 40 years.

While the assessments included MADRS and CGI, the primary outcome was change from baseline to endpoint in MADRS total score, and I will provide data only for that outcome. As is usually the case, the modified ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup MADRS assessment. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with factors for treatment group, center, and treatment-by-center interaction, and with baseline score as the covariate. The overall analysis for MADRS was highly significant ( $p = 0.002$  for LOCF and  $p = 0.001$  for OC).

#### Efficacy Results on MADRS Total Score for 99001 (LOCF)

	Baseline MADRS	Week 8 MADRS	[P-value(vs pbo)]
Escitalopram 10 mg	29	-16.3	0.002
Placebo	29	-13.6	

For the LOCF analysis, the sponsor did not, in fact, always use the last value for imputed values. Rather, they used a rule to select best fit observations for missing values. Nevertheless, the results of the true LOCF analyses conducted by Dr. Chen yielded similar and also highly significant results.

While not described here, results on various secondary endpoints also generally favored both escitalopram over placebo.

Comment: Both Drs. Alfaro and Chen considered this a positive study, and I agree.

### 5.1.2.2 Study 99003

This was a randomized, double-blind, parallel group, 8-week, flexible-dose multicenter study (69 non-US sites, including Belgium, Canada, Finland, France, Norway, Sweden, Switzerland, and the UK) comparing escitalopram immediate release tablets (10 to 20 mg/day, taken as a single am or pm dose), citalopram immediate release tablets (20 to 40 mg/day, taken as a single pm dose), and placebo in adult outpatients meeting DSM-IV criteria for MDD. Patients were started at 10 mg (for escitalopram) or 20 mg (for citalopram), and doses were increased to the higher dose at week 4 or 6, as needed. There were roughly 155 patients per each of the 3 groups in the sample

analyzed (n=468), with the % completing to 8 weeks ranging from 90 to 95%. The patients were about 3/4 female, essentially all Caucasian, and the mean age was 43 years. The mean escitalopram dose for completers was 14 mg/day.

While the assessments included MADRS and CGI, the primary outcome was change from baseline to endpoint in MADRS total score, and I will provide data only for that outcome. As is usually the case, the modified ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup MADRS assessment. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with factors for treatment group, center, and treatment-by-center interaction, and with baseline score as the covariate. The overall analysis (escitalopram vs placebo) for MADRS was highly significant (p = 0.002 for LOCF and p = 0.009 for OC). It is of interest that the citalopram vs placebo comparison was not significant.

#### **Efficacy Results on MADRS Total Score for 99003 (LOCF)**

	<b>Baseline MADRS</b>	<b>Week 8 MADRS</b>	<b>[P-value(vs pbo)]</b>
<b>Escitalopram 10-20 mg</b>	<b>29</b>	<b>-15.1</b>	<b>0.002</b>
<b>Citalopram 20-40 mg</b>	<b>29</b>	<b>-13.7</b>	<b>0.109</b>
<b>Placebo</b>	<b>29</b>	<b>-12.2</b>	

For the LOCF analysis, the sponsor did not, in fact, always use the last value for imputed values. Rather, they used a rule to select best fit observations for missing values. Nevertheless, the results of the true LOCF analyses conducted by Dr. Chen yielded similar and also highly significant results.

While not described here, results on various secondary endpoints also generally favored both escitalopram over placebo.

Comment: Both Drs. Alfaro and Chen considered this a positive study, and I agree.

#### **5.1.3 Comment on Other Important Clinical Issues Regarding Escitalopram for MDD**

##### Evidence Bearing on the Question of Dose/Response for Efficacy

Neither of these studies sheds any additional light on the issue of dose response. In the study supporting the original NDA, there appeared to be no advantage in the 20 mg escitalopram dose over the 10 mg dose, and this finding is reflected in labeling. Study 99001 provides additional evidence in support of the 10 mg dose. Thus, there is no basis for changing recommendations regarding dosing, i.e., that 10 mg should be the usual dose, but patients not responding at a 10 mg dose may be advanced to 20 mg, along with the qualification that the available data do not support any advantage of the higher dose in the average patient.

##### Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender and age. There were too few non-Caucasian patients to justify an analysis based on race. The sponsor's

analyses of a pool of studies 99001 and 99003 gave no indication of differences in response based on gender and age, while our statistician's analysis of individual studies suggested a possible interaction, i.e., more effect in females and in younger patients. It's difficult to know how to interpret these findings, especially since the differences in effect sizes for the subgroups do not differ much in the pooled analyses, which I consider the more appropriate ones. Thus, I am not inclined to view this as a signal of differential response worth noting in labeling. We did not see any such signal for the earlier study with escitalopram.

#### Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the MADRS observed in studies 99001 and 99003 were similar to that seen in other positive antidepressant trials, and I consider this a sufficient effect to support an antidepressant claim for this product based solely on studies with escitalopram.

#### Duration of Treatment

The sponsor has already submitted supporting the long-term efficacy of escitalopram, and this information is already included in labeling.

#### **5.1.4 Conclusions Regarding Efficacy Data**

The sponsor has, in my view, provided sufficient evidence to support the claim that short-term antidepressant efficacy for escitalopram can be based on studies done solely with escitalopram.

#### **5.2 Safety Data**

The safety data from studies 99001 and 99003 were included in the original NDA for Lexapro and reviewed at that time, along with all other Lexapro safety data. Thus, labeling already reflects the safety data from those studies. The only additional safety data for escitalopram included in this supplement were the results from the alcohol interaction study, SCT-MD-10. Dr. Alfaro reviewed the data from this study, and agreed that, as was true of the original alcohol interaction studies with citalopram, there was no apparent interaction.

#### **5.3 Clinical Sections of Labeling**

We have modified the clinical sections of the draft labeling that is included with the approvable letter. We have added recently developed language for the SSRI class regarding bleeding related adverse events, discontinuation symptoms, and neonatal adverse events. The explanations for the changes are provided in bracketed comments in the draft labeling.

#### **6.0 WORLD LITERATURE**

There were no literature reports provided by the sponsor in this supplement, and we will ask for a world literature update on escitalopram in the approvable letter.

## **7.0 FOREIGN REGULATORY ACTIONS**

I am not aware of any adverse regulatory actions regarding escitalopram in other countries, however, we will ask for an update on the regulatory status of escitalopram for the treatment of MDD in the approvable letter.

## **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We decided not to take this NDA to the PDAC.

## **9.0 DSI INSPECTIONS**

Inspections were conducted at 2 foreign sites for these escitalopram studies (Drs. Wade and Sild). Although the final report for these inspections is not yet completed, it is my understanding that the data for both sites have been deemed acceptable.

## **10.0 LABELING AND APPROVABLE LETTER**

### **10.1 Final Draft of Labeling Attached to Approvable Package**

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's most recent draft dated 2-6-03.

### **10.2 Approvable Letter**

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

I believe that Forest has submitted sufficient data to support the conclusion that the antidepressant effectiveness of escitalopram can be based on studies done solely with escitalopram. I recommend that we issue the attached approvable letter with our labeling proposal in anticipation of final approval.

cc:

Orig NDA 21-323/S-007

HFD-120

HFD-120/TLaughren/RKatz/PAndreason/CAlfaro/PDavid

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/s/

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Thomas Laughren  
11/12/03 12:26:32 PM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-323/S-007 & 21-365/S-001**

**CHEMISTRY REVIEW(S)**

HEMIST REVIEW  
OF SUPPLEMENT 1

1. ORGANIZATION: HFD-120  
2. NDA Number: 21-323  
3. SUPPLEMENT NUMBERS/DATES: SE8-007  
Letter date: February 6, 2003  
Stamp date: February 7, 2003  
4. AMENDMENTS/REPORTS/DATES: SE8-007(BC)  
Letter date: July 11, 2003  
Stamp date: July 14, 2003  
5. RECEIVED BY CHEMIST: March 27, 2003

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

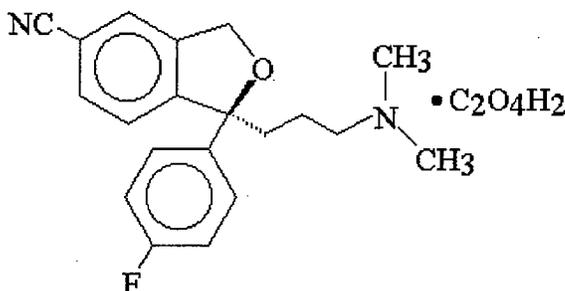
8. NONPROPRIETARY NAME:

Escitalopram oxalate

9. CHEMICAL NAME/STRUCTURE:

S (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobezofuran-5-carbonitrile, hydrogen oxalate

MW: 414.42, C<sub>20</sub>H<sub>21</sub>FN<sub>2</sub>O · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>



10. DOSAGE FORM(S):

Coated Tablet

11. POTENCY:

5 mg, 10 mg, 20 mg

12. PHARMACOLOGICAL CATEGORY:

Antidepressant

13. HOW DISPENSED:

(Rx)  (OTC)

14. RECORDS & REPORTS CURRENT:

Yes  No

REVIEW RECORDS & REPORTS CURRENT

Yes  No

15. RELATED IND/NDA/DMF: NA

16. SUPPLEMENT PROVIDES FOR: The efficacy study results from Studies 99001 and 99003, which evaluated the efficacy and safety of Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg and 20 mg for the treatment of major depression disorder.

17. COMMENTS:

Included in this submission are final study reports for the following studies:

- 1) Study 99001: "A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg escitalopram in outpatients with major depression disorder"
- 2) Study 99003: "A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of escitalopram in outpatients with major depressive disorder"
- 3) Study SCT-10: "Placebo-controlled Crossover Study of the Psychomotor Effects of Escitalopram with and without Alcohol Co-administration"

During the initial NDA review of 21-323 (tablets) the Medical Reviewer (Karen Brugge, M.D. (HFD-120)) noted that these studies were positive. Since the final study reports came in after the initial application, statistical review of these studies was not possible, and the NDA was approved on one study, SCT-MD-01. Forest Laboratories is now submitting the final study reports for Study 99001 and Study 99003. Forest is also including the final study report for Study SCT-MD-10 ("Placebo-controlled Crossover Study of the Psychomotor Effects of escitalopram with and without Alcohol Co-administration").

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 Forest Laboratories, for NDA 21-323/SE8-007 (tablets) is claiming categorical exclusion from Environmental Assessment on this action. On July 11, 2003 Forest Laboratories submitted supplemental amendment 21-323/SE8-007(BC) in response to the July 2, 2003 telephone conversation. In their July 11, 2003 supplemental amendment Forest Laboratories stated that FDA approval of supplement NDA 21-323/SE8-007 will not significantly increase the use of the active moiety, and that Forest claims categorical exclusion from environmental assessment under 21 CFR 25.31(a).

The three studies listed above are described by Forest Laboratories placebo-controlled trials. The sponsor has included in the Annual report (June 28, 2002 to June 27, 2003) for IND 58,380 (Escitalopram Tablets) the specifications for the following clinical drug product:

- 1) Encapsulated Escitalopram Tablets, 10 mg and 20 mg (Ref. No. PRD-816-04)
- 2) Non-trade Citalopram Tablets, 0 mg and  
Non-Trade Escitalopram Tablets, 0 mg (Ref. No. SCIT-TABPL-SPEC-08)

The two specifications sheets listed above are appended to this review. The sponsor has adequately described and release tested the clinic drug product and placebo for the studies described above. The analytical test methods listed in the specification sheets describing the clinic drug product and placebo are identical to the analytical procedures approved in the NDA for Lexapro™ Tablets, NDA 21-323, dated March 23, 2001 and approved on August 14, 2002.

18. CONCLUSIONS & RECOMMENDATIONS: Recommend issuing approval letter.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
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Lorenzo A. Rocca

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

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CC:

NDA 21-323/SE8-007  
HFD-120/Division File  
HFD-120/TOliver  
HFD-120/LRocca  
HFD-120/PDavid

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Chemistry Review

21-323 /S-007

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Lorenzo Rocca  
10/28/03 04:24:58 PM  
CHEMIST

Thomas Oliver  
10/29/03 08:44:17 AM  
CHEMIST

CHEMIST REVIEW  
OF SUPPLEMENT 1

1. ORGANIZATION: HFD-120  
2. NDA Number: 21-365  
3. SUPPLEMENT NUMBERS/DATES: SE8-001  
Letter date: February 6, 2003  
Stamp date: February 7, 2003  
4. AMENDMENTS/REPORTS/DATES: SE8-001(BC)  
Letter date: July 11, 2003  
Stamp date: July 14, 2003  
5. RECEIVED BY CHEMIST: March 27, 2003

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) Oral Solution, 5mg/5mL

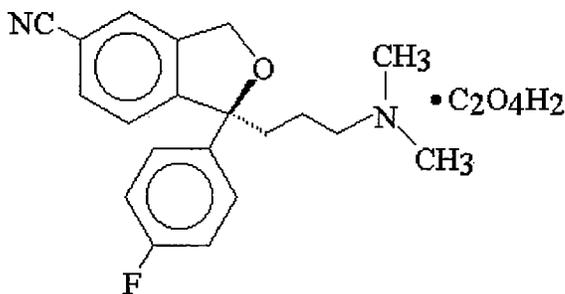
8. NONPROPRIETARY NAME:

Escitalopram oxalate

9. CHEMICAL NAME/STRUCTURE:

S (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobezofuran-5-carbonitrile, hydrogen oxalate

MW: 414.42, C<sub>20</sub>H<sub>21</sub>FN<sub>2</sub>O · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>



10. DOSAGE FORM(S):

Oral Solution

11. POTENCY:

5mg/5mL

12. PHARMACOLOGICAL CATEGORY:

Antidepressant

13. HOW DISPENSED:

(Rx)  (OTC)

14. RECORDS & REPORTS CURRENT:

Yes  No

REVIEW RECORDS & REPORTS CURRENT

Yes  No

15. RELATED IND/NDA/DMF: NA

16. SUPPLEMENT PROVIDES FOR: The efficacy study results from Studies 99001 and 99003, which evaluated the efficacy and safety of Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg and 20 mg for the treatment of major depression disorder.

17. COMMENTS:

Included in this submission are final study reports for the following studies:

- 1) Study 99001: "A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg escitalopram in outpatients with major depression disorder"
- 2) Study 99003: "A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of escitalopram in outpatients with major depressive disorder"
- 3) Study SCT-10: "Placebo-controlled Crossover Study of the Psychomotor Effects of Escitalopram with and without Alcohol Co-administration"

During the NDA review of 21-323 (Lexapro™ (escitalopram oxalate) Tablets 5 mg, 10 mg and 20 mg) the Medical Reviewer (Karen Brugge, M.D. (HFD-120)) noted that these studies were positive. Since the final study reports came in after the initial application, statistical review of these studies was not possible, and NDA 21-323 was approved on one study, SCT-MD-01. Forest Laboratories is now submitting the final study reports for Study 99001 and Study 99003. Forest is also including the final study report for Study SCT-MD-10 ("Placebo-controlled Crossover Study of the Psychomotor Effects of escitalopram with and without Alcohol Co-administration"). Since Lexapro™ (escitalopram oxalate) Oral Solution, 5mg/5mL has been shown to be bioequivalent to the tablet formulation the sponsor has submitted the efficacy and safety results from Studies 99001, 99003 and SCT-10 to NDA 21-365 Lexapro™ (escitalopram oxalate) Oral Solution, 5 mg/5 mL.

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 Forest Laboratories, for NDA 21-365/SE8-001 (Lexapro™ (escitalopram oxalate) Oral Solution, 5mg/5mL) is claiming categorical exclusion from Environmental Assessment on this action. On July 11, 2003 Forest Laboratories submitted supplemental amendment 21-365/SE8-001(BC) in response to the July 2, 2003 telephone conversation. In their July 11, 2003 supplemental amendment Forest Laboratories stated that FDA approval of supplement NDA 21-365/SE8-001 will not significantly increase the use of the active moiety, and that Forest claims categorical exclusion from environmental assessment under 21 CFR 25.31(a).

18. CONCLUSIONS & RECOMMENDATIONS: Recommend issuing approval letter.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
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Lorenzo A. Rocca

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

cc:  
NDA 21-365/SE8-001  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-323/S-007 & 21-365/S-001**

**STATISTICAL REVIEW(S)**



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

## STATISTICAL REVIEW AND EVALUATION Clinical Studies

NDA/Serial Number: 21-323/SE8-007 & 21-365/SE8-001  
Drug Name: Lexapro<sup>TM</sup>  
(escitalopram oxalate) Tablets and Oral Solution  
Indication: Major Depressive Disorder  
Applicant: Forest Laboratories, Inc  
Date(s): Date of Document: 02/06/2003  
PDUFA Due Date: 12/07/2003  
Review Priority: Standard  
Biometrics Division: Division of Biometrics I, HFD-710  
Statistical Reviewer: Yeh-Fong Chen, Ph.D.  
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## **1 Executive Summary of Statistical Findings**

The sponsor's analysis results for both studies 99001 and 99003 are confirmed and this reviewer agrees with the sponsor that the data support the escitalopram's efficacy.

When both studies were evaluated for efficacy, this reviewer was able to confirm the sponsor's analysis results for all efficacy endpoints for all visits by both observed case analysis and LOCF analysis. However, since the sponsor did not simply use the last available evaluable visit observations to impute the missing values for the last visit, (instead they used a rule to choose a best fit observation for each patient to impute missing observations), their analysis results were different from the reviewer's LOCF analysis results. Nevertheless, this reviewer found that the differences were not large enough to affect the final conclusions.

### **1.1 Recommendations and Conclusions**

After carefully evaluating the sponsor's submission and analysis results, this reviewer agrees with the sponsor that for both studies the data support the escitalopram's efficacy.

### **1.2 Brief Overview of Clinical Studies**

The sponsor submitted final study reports for two pivotal studies: 99001 and 99003 to demonstrate the escitalopram's efficacy in treating patients with major depressive disorder. Study 99001 was designed as a double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg escitalopram in outpatients with major depressive disorder. Study 99003 was designed similarly to Study 99001 but instead of using 10 mg escitalopram, it used flexible dosages.

For both studies, the primary efficacy endpoint was the change from baseline to last assessment of the MADRS total score. It was analyzed by the analysis of covariance with factors for treatment group, collective centers, and the baseline score as a covariate by the last observation carried forward (LOCF) analysis. Since the LOCF analysis results for the primary and most secondary variables demonstrated significantly greater improvement in the escitalopram treated patients at the end of Week 8, the sponsor concluded that both studies demonstrated efficacy of escitalopram 10-20 mg/day for the treatment of major depressive disorder.

### **1.3 Statistical Issues and Findings**

This reviewer confirmed the sponsor's analysis results for all efficacy endpoints for all visits for both the observed case and LOCF analyses. However, since the sponsor did not simply use the last available evaluable visit observation to impute the missing values for last visit, (instead they used a rule to choose most suitable observations to impute the missing values) their analysis results were different from the reviewer's LOCF analysis results. These differences were, however, not large enough to affect the final conclusions.

## 2 Introduction

### 2.1 Overview

Included in this submission, the sponsor submitted final study reports for two pivotal studies: 99001 and 99003. Study 99001 is titled as “A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg escitalopram in outpatients with major depressive disorder”. Study 99003 is titled as “A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of escitalopram and citalopram in outpatients with major depressive disorder”.

For both studies, the primary efficacy endpoint was the change from baseline to last assessment of the MADRS total score. It was analyzed by the analysis of covariance with factors for treatment group, collective centers, and the baseline score as a covariate by the last observation carried forward (LOCF) analysis.

Table 1.1 shows the sponsor’s efficacy analysis results for the primary endpoint for both studies. As we can observe from the following table, in both studies, the LOCF analysis results for the mean change in the MADRS total score from baseline to the end of Week 8 showed significantly greater improvement in the escitalopram group compared to placebo. The LOCF analyses for most secondary variables also demonstrated significantly greater improvement in the escitalopram treated patients at the end of Week 8. So the sponsor concluded that both studies demonstrated efficacy of escitalopram 10-20 mg/day for the treatment of major depressive disorder.

Table 1.1 Sponsor’s Efficacy Analysis Results for the MADRS Total Score at Last Visit (Week 8) by LOCF

Study	Variable	Least Squares Means	SE	95% C.I.		P-value
				Lower	Upper	
99001	PBO (n=188)	-13.60	0.69	-14.96	-12.24	
	ESC (n=189)	-16.27	0.69	-17.63	-14.92	
	ESC-PBO	-2.68	0.85	-4.34	-1.01	0.002
99003	PBO (n=154)	-12.11	0.67	-13.44	-10.78	
	ESC (n=155)	-15.02	0.67	-16.35	-13.69	
	ESC-PBO	-2.91	0.93	-4.73	-1.09	0.002

### 2.2 Data Sources

The data can be found in the electronic document room (EDR) by the following directory: \\CDSESUB1\N21323\S\_007\2003-02-06\CRT.

### **3 Statistical Evaluation**

#### **3.1 Evaluation of Efficacy**

##### **3.1.1 Description of the Sponsor's Study 99001**

This study is titled as "A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg LU 26-054 in outpatient with Major Depressive Disorder". There were 40 centers in 5 countries (3 in Canada, 4 in Estonia, 27 in France, 5 in the Netherlands and 1 in the United Kingdom) participated.

##### **3.1.1.1 Study Objectives**

The objectives of the study were to compare the efficacy and safety of a fixed dose of 10mg escitalopram with that of placebo in outpatients with Major Depressive Disorder.

##### **3.1.1.2 Overall Study Design**

This study was a multinational, multicenter, phase III study with a randomized, double-blind, parallel-group, placebo-controlled, fixed-dose design.

There was a 1-week, single-blind run-in period with placebo, followed by an 8 week, double-blind treatment phase with escitalopram or placebo. Thirty days after the last dosing, a follow-up safety assessment was performed for patients who chose not to participate in a separate 12-month safety follow-up study.

Patients from a primary care setting were recruited from each investigator's group of patients, except for patients in Estonia and the Netherlands, who were referred to the centers by their general practitioner.

Patients were instructed to take the tablets at home at the same time every day (morning or evening). In the 1-week single-blind run-in period all patients took one placebo tablet daily. In the 8-week double-blind phase, the patients randomized to escitalopram treatment took one tablet daily containing 10mg escitalopram, while patients randomized to placebo treatment took one placebo tablet daily.

##### **3.1.1.3 Efficacy Assessments**

The primary measure of efficacy was based on the MADRS total score. The secondary measures of efficacy were based on the CGI-S and CGI-I scores.

##### **Montgomery and Asberg Depression Rating Scale (MADRS)**

The Montgomery and Asberg Depression Rating Scale consists of ten items, each with ratings on a scale from 0 (no symptoms) to 6 (severe symptoms). All the items are core

symptoms of the depressive episode and thus measure the severity of the depressive episode for the previous 7 days.

The MADRS ratings were based on a clinical interview with the patient beginning with general questions about symptoms and gradually becoming more detailed to allow for a precise rating of depression severity. The MADRS score was assessed at all visits, including an early termination visit, but not at the 30-day safety follow-up visit.

The ratings were carried out by the same person at each visit, whenever possible. Only persons experienced with MADRS rating and trained as raters during a co-rating session were allowed to rate patients on the MADRS. The rater sessions were undertaken to increase the interrater reliability, and were chaired by an experienced physician rater. At these sessions, video tapes were shown of patients with Major Depressive Disorder and the ratings were discussed.

### **Clinical Global Impressions Scales (CGI)**

The Clinical Global Impressions Scale consists of two sub-scales:

- Clinical Global Impressions Improvement Scale (CGI-I). This single-item rating scale evaluates a patient's total improvement from baseline on a defined 7-point scale regardless of whether the improvement is related to the study product. The investigator (rater) rated the patient from 1 (very much improved) to 7 (very much worse). CGI-I was rated at Weeks 1, 2, 3, 4, 6, and 8 (or an early termination visit).
- Clinical Global Impressions Severity Scale (CGI-S). This single-item rating scale evaluates a patient's severity of depression on a defined 7-point scale based on the investigator's total clinical experience with depressed patients. The investigator (rater) rated the patient from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). CGI-S was rated at Weeks 0, 1, 2, 3, 4, 6 and 8 (or an early termination visit).

#### **3.1.1.4 Statistical Methodology**

##### **Sample Size Calculations**

A minimum of 320 patients (160 in each treatment group) for the full-analysis set was expected to provide an approximate power of 85% to detect a significant difference in mean change from baseline to final assessment in the MADRS total score between the escitaloram and placebo groups. This assumed a signal-to-noise ratio of 0.33 at a significance level of 5%. The signal-to-noise ratio is the treatment group difference (mean change from baseline for escitalopram versus placebo) divided by the pooled standard deviation.

## **Analysis Sets and Patient Disposition**

The following analysis populations were defined both in the study protocol and the Statistical Analysis Plan (SAP):

- *all-patient-randomized set* (APRS) --- all patients randomized in the study
- *all-patient-treated set* (APTS) --- all randomized patients who took at least one dose of double-blind study product
- *full analysis set* (FAS) --- all randomized subjects who took at least one dose of double-blind study product and who had at least one post-baseline assessment of the MADRS total score
- *per-protocol set* (PPS) --- all randomized patients who had no major protocol violations, who received double-blind investigational product at least up to the Week 4 visit, and who had at least one assessment of the MADRS total score at or after this visit.

All efficacy analyses were conducted on the full-analysis set. If appropriate, additional efficacy analyses were to have been conducted on the per protocol set. All safety analyses were conducted on the all-patients-treated set.

The number of withdrawn patients was tabulated by the reason of withdrawal, and other variables considered relevant for describing withdrawals by treatment group. The relation of withdrawal to treatment duration, and other variables such as dose, sex, age, and the various diagnostic characteristics, was examined using a logistic regression or a Cox regression, as appropriate.

## **Baseline Characteristics of Treatment Groups**

The demographics and other initial characteristics of the patient population, including baseline depression rating scores and medical history at screening (including any concurrent illnesses), were summarized and displayed for each treatment group using descriptive statistical techniques. Statistical analyses (ANOVA and CHISQ) were performed to test for differences in baseline characteristics between treatment groups in MADRS total score, CGI-S score, age, sex, weight, and body mass index (BMI). Concurrent illnesses ongoing at baseline were coded and presented according to the terminology in International Classification of Disease, version 10 (ICD-10).

### **3.1.1.5 Efficacy Endpoints**

#### **Primary Efficacy Endpoint**

The primary efficacy endpoint was:

- The change from baseline to last assessment of the MADRS total score using the principle of last observation carried forward (LOCF) and applying the Week 8 visit window as described in the SAP.

## **Secondary Efficacy Endpoints**

The secondary efficacy endpoints were:

- MADRS total score at each visit
- Proportion of patients with at least a 50% reduction of the MADRS total score from baseline per visit (responders)
- Proportion of patients with a MADRS total score  $\leq 12$  per visit (complete remission)
- CGI-S score per visit and at Week 8
- Change from baseline to each visit of CGI-S score and at Week 8 (LOCF)
- Proportion of patients with a CGI-S score  $\leq 2$  per visit
- CGI-I score per visit and at Week 8 (LOCF)
- Proportion of patients with a CGI-I score  $\leq 2$  per visit and at Week 8 (LOCF)
- Change from baseline to final assessment of MADRS single items

### **3.1.1.6 Analyses of Efficacy Parameters**

#### **Primary Efficacy Analysis**

The primary efficacy analysis of the change in MADRS total score from baseline was based on a general linear model, using both treatment groups, for analysis of covariance (ANCOVA) with factors for treatment group, collective centers, and treatment by collective centers interaction, and with baseline score as a covariate. All centers that did not contribute to both treatment groups and did not contribute with at least 4 patients in the full-analysis set were merged into a single collective center. The following test procedure was used:

##### **Step 1**

Initially the model with treatment by center interaction was fitted. If the p-value for the F-test of the interaction was insignificant at the 10% level, then Step 2 was performed.

##### **Step 2**

The non-significant interaction term was removed from the initial model. In the resulting model the test of primary interest, escitalopram versus placebo, was performed on a 5% level.

The final model was evaluated by inspection and analysis of residuals, by comparing variability between treatment groups, and evaluating the potential influence of covariates.

#### **Secondary Efficacy Analyses**

The MADRS total score per visit was analyzed by ANCOVA using a model as in Step 2 above. In general, the CGI-S and CGI-I scores were analyzed in the same way as the MADRS total score in the primary analysis. However, the final CGI-S and CGI-I scores

were also analyzed using the non-parametric Cochran-Mantel-Haenszel mean score statistic with modified ridit scores and with individual centers comprising the strata. Between-group comparisons of the proportion of patients considered to be treatment responders were performed using  $\chi^2$  tests for the following:

- At least 50% reduction in the MADRS total score from baseline to visit; MADRS total score  $\leq 12$  per visit; CGI-S score  $\leq 2$  per visit; CGI-I score  $\leq 2$  per visit

The final changes in MADRS single items from baseline were analyzed by ANCOVA using a model as in Step 2, above.

### **3.1.1.7 Handling of Missing Data and Withdrawals**

In general, for analyses using LOCF, missing values for post-baseline MADRS, CGI-I, and CGI-S assessments were imputed by the value observed immediately prior to the missing value. The observed assessment used in “last assessment” LOCF analysis was not necessarily the absolutely last assessment for the patient, but could actually be the observed assessment that best fit the Week 8 visit window\*. If the number of missing MADRS items was less than two, the total score was calculated as: the sum of non-missing items times the total number of items divided by the number of non-missing items. If more than three items were missing, the total MADRS score was regarded as missing.

### **3.1.2 Description of the Sponsor’s Study 99003**

This study is titled as “A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of Lu 26-054 and citalopram in outpatients with Major Depressive Disorder.” There were 69 centers in 8 countries (3 in Canada, 22 in France, 17 in the United Kingdom, 3 in Belgium, 10 in Finland, 4 in Switzerland, 2 in Sweden and 8 in Norway) participated.

#### **3.1.2.1 Study Objectives**

The objectives of the study are to compare the efficacy and safety of escitalopram (Lu 26-054), independent of dose, in the interval of 10 to 20mg daily with that of placebo and a reference drug citalopram (20 to 40mg daily) in outpatients with Major Depressive Disorder.

#### **3.1.2.2 Overall Study Design**

This study was a multinational, multicenter, phase III study with a randomized, double-blind, parallel-group, placebo-controlled, flexible-dose design. There was a 1-week, single-blind run-in phase with placebo, followed by an 8-week, double-blind treatment phase with escitalopram, citalopram, or placebo. The initial doses were 10mg

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\* This sentence was stated in the sponsor study report but was not shown in the sponsor’s protocol or Statistical Analysis Plan.

escitalopram and 20mg citalopram. At Week 4 or Week 6, investigators had the option of doubling a patient's dosage of study product if his/ her response had been unsatisfactory or if there was an aggravation of the depression based on the CGI-S score. Investigator(s) could decrease the dosage to the original dosage at any time, after the increase in dosage, because of adverse events. Thirty days after last dosing, a follow-up safety assessment was performed for patients who chose not to participate in a separate 12-month safety follow-up study.

### **3.1.2.3 Efficacy Assessments**

Same as Study 99001 described in Section 3.1.1.3.

### **3.1.2.4 Statistical Methodology**

#### Sample Size Calculations

A minimum of 360 patients (120 patients in each treatment group) for the full-analysis set was expected to provide a power of at least 85% to detect a significant difference in mean change from baseline to final assessment in the MADRS total score between the escitalopram and placebo treatment groups. This assumed a signal-to-noise ratio of 0.40 at a significance level of 5%. The signal-to-noise ratio is the treatment group difference (mean change from baseline for escitalopram versus placebo) divided by the pooled standard deviation.

#### Analysis Sets and Patient Disposition

Same as Study 99001 described in Section 3.1.1.3

#### Baseline Characteristics of Treatment Groups

Same as Study 99001 described in Section 3.1.1.3

### **3.1.2.5 Efficacy Endpoints**

Same as Study 99001 described in Section 3.1.1.5

### **3.1.2.6 Analyses of Efficacy Parameters**

Same as Study 99001 described in Section 3.1.1.6

### **3.1.2.7 Handling of Missing Data and Withdrawals**

Same as Study 99001 described in Section 3.1.1.7

### 3.1.3 Sponsor's Efficacy Analysis Results for Study 99001

#### 3.1.3.1 Study Patients and Reasons of Withdrawals

Table 3.1 summarizes the patient disposition and the data sets used for the analyses. A total of 380 patients were randomized into the study (APRS) and of these, 320 patients completed the study (160 patients in each treatment group). All patients in the APRS took at least one dose of double-blind treatment and thus comprised the all patients treated set (APTS). Three patients in the escitalopram group were withdrawn after the first dose but prior to the first post-baseline MADRS assessment. Thus, a total of 377 patients comprised the full analysis set (FAS), which is the data set that all efficacy analyses were based on.

Table 3.1. Summary of Patient Disposition in the All-Patient-Randomized Set for Study 99001

	Placebo n (%)	Escitalopram n (%)	Total n (%)
Patients Randomized	189	191	380
Patients Treated	189	191	380
Patients Completed	160 (84.7)	160 (83.8)	320 (84.2)
Patients Withdrawn from APTS	29 (15.3)	31 (16.2)	60 (15.8)
Patient Data Sets:			
All Patients Treated Set (APTS)	189	191	380
Full Analysis Set (FAS)	189	188	377
Per Protocol Set (PPS)	160	167	327

Table 3.2 tabulates the frequencies of patients withdrawn from the study by primary reason. Overall, the most common primary reasons for withdrawal were lack of efficacy (n=20) and adverse events (n=11). Withdrawal due to lack of efficacy was more common in the placebo group (6.9%) compared to the escitalopram group (3.7%), whereas adverse events comprised the most common reason for withdrawal in the escitalopram group (4.7%) as compared to the placebo group (1.1%). Statistical analyses showed no significant differences between the two treatment groups for time to withdrawal for all reasons, for time to withdrawal due to AEs, or for time to withdrawal due to lack of efficacy.

Table 3.2 Withdrawals from Study by Primary Reason in the All-Patient-Treated Set for Study 99001

	Treatment Groups				Total	
	PBO		ESC			
	n	(%)	n	(%)	n	(%)
Patients Treated	189		191		380	
Patients Withdrawn	29	(15.3)	31	(16.2)	60	(15.8)
Primary Reason:						
Adverse Event(s)	2	(1.1)	9	(4.7)	11	(2.9)
Lack of efficacy	13	(6.9)	7	(3.7)	20	(5.3)
Non-compliance with study	0	(0.0)	0	(0.0)	0	(0.0)
medication						
Protocol violation	2	(1.1)	4	(2.1)	6	(1.6)
Withdrawal of consent	3	(1.6)	6	(3.1)	9	(2.4)
Lost to follow up	6	(3.2)	3	(1.6)	9	(2.4)
Administrative reason(s)	0	(0.0)	0	(0.0)	0	(0.0)
Other reason(s)	3	(1.6)	2	(1.0)	5	(1.3)

### 3.1.3.2 Baseline Comparability of Treatment Groups

The patient demographic values at baseline are summarized in Table 3.3. In the study, there was an approximately 3 to 1 ratio of women to men, and almost all the patients were Caucasian. The demographic values were approximately similar for the escitalopram and placebo groups. There were no statistically significant imbalances in age or sex between the treatment groups.

Table 3.3 Summary of Patient Demographics in the All-Patient-Treated Set for Study 99001

		Treatment Groups					
		PBO		ESC		Total	
		stats	(%)	stats	(%)	stats	(%)
Patients Treated	n	189		191		380	
Sex	Male	42	(22.2)	50	(26.2)	92	(24.2)
	Female	147	(77.8)	141	(73.8)	288	(75.8)
Age (yrs.)	n	189		191		380	
	Mean	40		41		40	
	Median	40		41		40	
	SD	12		11		11	
	Min.	18		18		18	
	Max.	65		65		65	
Race	Caucasian	185	(97.9)	188	(98.4)	373	(98.2)
	Black	0	(0.0)	1	(0.5)	1	(0.3)
	Asian	0	(0.0)	0	(0.0)	0	(0.0)
	Other	4	(2.1)	2	(1.0)	6	(1.6)

For baseline efficacy parameters, at baseline, approximately 90% of the patients were moderately ill (MADRS from 22 to 34) and approximately 10% of the patients were severely ill (MADRS  $\geq$  35, although none of the patients with a MADRS total score  $>$ 40 were to be enrolled in this study). The mean MADRS total score at baseline was approximately 29, and the mean CGI-S score at baseline was approximately 4.4 for each treatment group. The treatment groups were judged to be clinically similar at baseline and no statistically significant differences were observed.

### 3.1.3.3 Efficacy Evaluation

All efficacy analyses were conducted on the full-analysis set. No efficacy analyses were conducted for the per-protocol set since the number of patients in this set did not differ from that in the full-analysis set by more than 20% specified in the SAP.

#### 3.1.3.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint was defined as the change in MADRS total score from baseline to last assessment using last observation carried forward method and applying

the Week 8 visit window\*. What the sponsor did was if the data were available on Week 8 visit window, then the one which is closer to Day 56 was chosen as the last observation, otherwise the last observation was used although it may not be the evaluable one in its specific window. (It is called LOCF in this review). Escitalopram was statistically significantly superior to placebo with an estimated difference in change of MADRS total score of 2.7 points greater than that for placebo. The least square means of MADRS total scores from baseline to the endpoint for individual treatment groups by the LOCF are shown in Table 3.4. The escitalopram group had the greatest improvement during the treatment period of 8 weeks compared to the placebo group.

Table 3.4 Treatment Difference of the Adjusted Mean Changes from Baseline in MADRS Total Score for Study 99001

Variable	Visit	Least Squares Means	SE	95% C.I.		P-value
				Lower	Upper	
PBO (n=189)	Last (LOCF)	-13.60	0.69	-14.96	-12.24	
ESC (n=188)	Last (LOCF)	-16.27	0.69	-17.63	-14.92	
ESC-PBO	Last (LOCF)	-2.68	0.85	-4.34	-1.01	0.002

Note: P-value was obtained by ANCOVA with treatment and center as factors and baseline score as a covariate.

Some statistical aspects about the primary efficacy analysis are summarized as follows.

#### Centers

Using the grouping rule described in the statistical analysis plan, centers 1103, 1104, 1113, 1115, 1122, 1302, 1312, 1313 and 1314 were merged into 9999. In total, there were 32 centers. Although there was no statistically significant treatment-by-center interaction, there was a statistically significant effect of center with p-value <0.0001. This meant that centers did behave differently, but the differences were independent of the treatment given.

#### Residuals and Test for Normality

Various checks of the model were performed. Although the calculated standardized residuals showed no systematic trends on a scatter plot against predicted values, the histogram of residuals showed tendencies of a skewed distribution, and the test for normality was rejected (p=0.037). The robustness of the chosen ANCOVA method against departures from normality, was, however, confirmed by additional analyses using ranks, non-parametric statistics, and transforming MADRS scores with the square root.

\* The sponsor pre-specified a table of time window for each scheduled visit in the Statistical Analysis Plan. The Week 8 visit window was defined from Days 50 to 63, but in SAP it says that 'The upper limit of the week 8 window may be extended to accommodate all data from that visit.'

### 3.1.3.3.2 Secondary Efficacy Endpoints

#### MADRS Adjusted Total Scores Per Visit

The difference of adjusted mean change of the MADRS total scores from baseline at each visit by OC between the escitalopram and the placebo are shown in Table 3.5. The adjusted mean change in MADRS total scores from baseline for individual treatment groups are shown in Table 6.1 of the appendices. As we can observe from the tables, there was a clear trend throughout the study for the mean change in MADRS total scores from baseline to be larger for the escitalopram group compared to those for the placebo group. Escitalopram was statistically significantly superior to placebo from Week 2 onwards for the estimated difference in adjusted change in mean MADRS total score including the last visit, which represents the primary efficacy endpoint. When using LOCF at each visit, a statistically significant difference between escitalopram and placebo was also seen from Week 2 onwards. So, the sponsor concluded that the similarity of the OC and LOCF analyses indicated the robustness of the model.

Table 3.5 Treatment Difference of the Adjusted Mean Changes from Baseline in MADRS Total Score for Study 99001

Treatment Difference	Visit #		Least Squares Mean	SE	95% Confidence Limits		p-value
					Lower	Upper	
ESC-PBO	Week 1	(OC)	-0.73	0.49	-1.70	0.24	0.141
	Week 2	(OC)	-1.87	0.64	-3.13	-0.60	0.004
	Week 3	(OC)	-2.77	0.73	-4.21	-1.32	0.000
	Week 4	(OC)	-2.46	0.75	-3.94	-0.99	0.001
	Week 6	(OC)	-3.64	0.85	-5.31	-1.98	0.000
	Week 8	(OC)	-2.69	0.81	-4.28	-1.11	0.001
	Last	(LOCF)	-2.68	0.85	-4.34	-1.01	0.002

#### Proportion of Patients with a $\geq 50\%$ Reduction in MADRS Total Score (Responders)

The difference of proportion of patients with  $\geq 50\%$  reduction in MADRS total score between escitalopram and placebo is shown in Table 3.6. The proportions of patients with at least a 50% reduction of the baseline MADRS total score (responders) for individual treatment groups by visit (OC) and last assessment (LOCF) are shown in Table 6.2 of the appendices. As we observe from the tables, the difference in the proportion of escitalopram-treated compared to placebo-treated patients who had a reduction of  $\geq 50\%$  in MADRS total score is statistically significant in favor of escitalopram at Weeks 4 to 8 (OC), and at the last visit (LOCF). When using LOCF by visit, the difference in the proportion of escitalopram-treated compared to placebo-treated patients was statistically significant in favor of escitalopram from Week 4 onward (values are not shown in this review). The similarity of the OC and LOCF analyses indicated the robustness of the model.

Table 3.6 Differences between Treatment Groups in the Proportion of Patients with  $\geq$  50% Reduction in MADRS Total Score for Study 99001

Treatment Difference	Visit #		MADRS $\geq$ 50% Reduction Resp.rate Dif. (%)	95% Confidence Limits		p-value
				Lower(%)	Upper(%)	
ESC-PBO	Week 1	(OC)	2.7	-1.8	7.1	0.347
	Week 2	(OC)	1.7	-5.7	9.2	0.661
	Week 3	(OC)	7.3	-2.5	17.2	0.169
	Week 4	(OC)	10.7	0.3	21.1	0.049
	Week 6	(OC)	17.1	6.4	27.8	0.002
	Week 8	(OC)	14.3	3.5	25.1	0.013
	Last	(LOCF)	13.5	3.5	23.5	0.010

#### Proportion of Patients in Complete Remission (MADRS Score $\leq$ 12)

The difference between the escitalopram and placebo group in the proportion of patients in remission (i.e., MADRS score  $\leq$  12) is shown in Table 3.7 and the proportions of patients in complete remission for individual treatment groups by visit are shown in Table 6.3 of the appendices. As it was shown in the tables, this difference was statistically significant in favor of escitalopram from Week 6 onwards (OC) including the last visit (LOCF).

Table 3.7 Difference between Treatment Groups in the Proportion of Patients with MADRS Scores  $\leq$  12 for Study 99001

Treatment Difference	Visit #		MADRS $\leq$ 12 Resp.rate Dif. (%)	95% Confidence Limits		p-value
				Lower(%)	Upper(%)	
ESC-PBO	Week 1	(OC)	2.7	-1.1	6.4	0.258
	Week 2	(OC)	5.3	-1.1	11.7	0.124
	Week 3	(OC)	3.9	-5.0	12.9	0.446
	Week 4	(OC)	8.4	-1.5	18.4	0.106
	Week 6	(OC)	16.1	5.6	26.6	0.004
	Week 8	(OC)	14.4	3.6	25.2	0.010
	Last	(LOCF)	13.5	3.7	23.3	0.009

#### CGI Severity Scores (Analyzed by ANCOVA)

The adjusted change in mean CGI-S scores from baseline for each treatment group by visit (OC) and last visit (LOCF) is shown in Table 6.4 of the appendices. The corresponding least square estimates difference between groups are shown in Table 3.8. As it was shown in the tables, for the observed case analysis, Escitalopram was statistically significantly superior to placebo ( $p \leq 0.05$ ) from Week 3 onwards. For the endpoint LOCF analysis, however, escitalopram was not statistically significantly superior to the placebo ( $p=0.054$ ).

Table 3.8 Treatment Difference of the Adjusted Mean Changes from Baseline in CGI Severity Score for Study 99001

Treatment Difference	Visit #		Least Squares Mean	SE	95% Confidence Limits		p-value
					Lower	Upper	
ESC-PBO	Week 1	(OC)	0.01	0.06	-0.11	0.13	0.828
	Week 2	(OC)	-0.16	0.08	-0.33	0.01	0.061
	Week 3	(OC)	-0.31	0.10	-0.51	-0.11	0.003
	Week 4	(OC)	-0.29	0.11	-0.51	-0.06	0.012
	Week 6	(OC)	-0.33	0.12	-0.57	-0.10	0.006
	Week 8	(OC)	-0.25	0.12	-0.49	-0.01	0.043
	Last	(LOCF)	-0.23	0.12	-0.46	0.00	0.054

Cochran-Mantel-Haenszel Analysis of CGI-S Score at Week 8 (LOCF)

A non-parametric Cochran-Mantel-Haenszel (CMH) test, with individual centers comprising the strata, showed a difference between the treatment groups' mean CGI-S scores but not statistically significant.

Proportion of Patients with CGI-S Scores of 1 or 2

The proportion of patients with a CGI-S score of 1 (normal, not at all ill), or 2 (borderline ill) by treatment group and visit is shown in Table 6.5 of the appendices and the differences between the escitalopram group and the placebo group are presented in Table 3.9. As it was shown in the tables, in general, a greater percentage of patients in the escitalopram group had CGI-S scores of 1 or 2 from Week 2 onwards (OC) compared to patients in the placebo group. However, the differences are not statistically significant.

Table 3.9 Differences between Treatment Groups in the Proportion of Patients with CGI Severity Scores of 1 or 2 for Study 99001

Treatment Difference	Visit #		CGI-S 1 or 2* Resp.rate Dif. (%)	95% Confidence Limits		p-value
				Lower(%)	Upper(%)	
ESC-PBO	Week 1	(OC)	-1.7	-4.9	1.5	0.336
	Week 2	(OC)	1.8	-4.0	7.6	0.567
	Week 3	(OC)	1.6	-7.6	10.9	0.803
	Week 4	(OC)	9.4	-1.0	19.7	0.083
	Week 6	(OC)	7.4	-3.4	18.2	0.217
	Week 8	(OC)	5.5	-5.5	16.5	0.367
	Last	(LOCF)	6.6	-3.3	16.5	0.209

CGI-I Improvement Scores (Analyzed by the ANCOVA)

The adjusted means of CGI-I scores for individual treatment groups by visit (OC) including last visit (LOCF) are shown in Table 6.6 of the appendices. The corresponding treatment differences in the adjusted means of CGI-I scores are shown in Table 3.10. Throughout the study the escitalopram group showed more improvement than the placebo group did. The escitalopram group was statistically significantly superior to the placebo group at all visits (OC) including last visit (LOCF) for the estimated difference in adjusted mean CGI-I score.

Table 3.10 Treatment Difference in the Adjusted Means of CGI Improvement Scores for Study 99001

Treatment Difference	Visit #		Least Squares Mean	SE	95% Confidence Limits		p-value
					Lower	Upper	
ESC-PBO	Week 1	(OC)	-0.19	0.09	-0.36	-0.01	0.035
	Week 2	(OC)	-0.20	0.09	-0.39	-0.02	0.032
	Week 3	(OC)	-0.42	0.10	-0.62	-0.21	0.000
	Week 4	(OC)	-0.22	0.10	-0.43	-0.02	0.035
	Week 6	(OC)	-0.40	0.12	-0.64	-0.16	0.001
	Week 8	(OC)	-0.32	0.11	-0.54	-0.10	0.004
	Last	(LOCF)	-0.33	0.12	-0.56	-0.09	0.006

Cochran-Mantel-Haenszel Analysis of CGI-I Score at Week 8 (LOCF)

A non-parametric Cochran-Mantel-Haenszel test, with individual centers comprising the strata, showed overall statistical differences among treatment group mean CGI-I scores (p=0.0076).

Proportion of Patients with CGI-Improvement Scores of 1 or 2

The proportions of patients with a CGI-I score of 1 (very much improved) or 2 (much improved) for individual treatment groups by visit are shown in Table 6.7 of the appendices. In general, a greater percentage of patients in the escitalopram group had CGI-I scores of 1 or 2 from Week 1 onwards compared to patients in the placebo group. The differences between treatment groups for escitalopram versus placebo are shown in Table 3.11. The escitalopram group was statistically significantly superior (Fisher's exact test, p≤0.05) to the placebo group from Week 3 onwards, but except Week 4 (OC) including last visit (LOCF), and from Week 2 onwards using the LOCF-by-visit data set. (Note: The LOCF-by-visit analysis was not show in this review.)

Table 3.11 Differences between Treatment Groups in the Proportion of Patients with CGI Improvement Scores of 1 or 2 for Study 99001

Treatment Difference	Visit #		CGI-I 1 or 2* Resp.rate Dif. (%)	95% Confidence Limits		p-value
				Lower(%)	Upper(%)	
ESC-PBO	Week 1	(OC)	6.3	-1.1	13.7	0.116
	Week 2	(OC)	7.9	-1.8	17.7	0.115
	Week 3	(OC)	11.9	1.4	22.4	0.031
	Week 4	(OC)	6.0	-4.4	16.4	0.269
	Week 6	(OC)	16.0	5.6	26.4	0.003
	Week 8	(OC)	11.1	0.8	21.4	0.044
	Last	(LOCF)	12.5	2.7	22.4	0.016

**3.1.3.4 Sponsor's Efficacy Conclusions**

The primary efficacy analysis showed a significantly superior therapeutic effect for escitalopram compared to placebo. The primary efficacy analysis showed a change in MADRS total score from baseline to Week 8 (LOCF) of 16.3 points in the escitalopram

group and 13.6 points in the placebo group. This difference of 2.7 points in favor of escitalopram was statistically significant.

In support of the primary analysis, escitalopram was statistically superior to placebo from Week 2 onwards (LOCF and OC) in the secondary analysis of the change in MADRS total score from baseline to each visit. The proportion of escitalopram responders, defined as a reduction of  $\geq 50\%$  on the MADRS total score, was statistically superior to that of placebo responders from Week 4 onwards (LOCF and OC). The proportion of escitalopram-treated patients in complete remission, defined as a MADRS total score  $\leq 12$ , was statistically superior to that of placebo-treated patients from Week 2 onwards (except Week 3) (LOCF), and from Week 6 onwards (OC).

Escitalopram was statistically superior to placebo on analyses of CGI-I from Week 2 onwards (LOCF) and at all assessments (OC). The proportion of very much or much improved patients on the CGI-I scale was statistically superior in the escitalopram group compared to the placebo group from Week 2 onwards (LOCF) and from Week 3 onwards (except Week 4) (OC). Furthermore, escitalopram was statistically superior to placebo on the CGI-S scale from Week 3 onwards (OC). For the endpoint LOCF analysis, however, escitalopram was not statistically significantly superior to the placebo ( $p=0.054$ ). The proportion of escitalopram-treated patients who had scores of 1 or 2 on the CGI-S scale was statistically superior to that of placebo-treated patients at Week 4 (LOCF), and only numerically superior to that of placebo from Week 2 onwards (OC).

### **3.1.3.5 Statistical Reviewer's Findings and Comments**

1. This reviewer confirmed the sponsor's analysis results for all efficacy endpoints for all visits by both observed case analysis and LOCF analysis. However, since the sponsor did not simply use the last available evaluable visit observations to impute the missing observations for the last visit, [instead, they used a rule (see Section 3.1.3.3.1) to choose a best fit observation to impute the missing observation for each patient], their analysis results were different from the reviewer's LOCF analysis results. Nevertheless, this reviewer found that the differences were not large enough to affect the final conclusions. In conclusion, this reviewer agrees with the sponsor that the data from this study support the escitalopram's efficacy.

### **3.1.4 Sponsor's Efficacy Analysis Results for Study 99003**

#### **3.1.4.1 Study Patients and Reasons of Withdrawals**

Patient disposition and the data sets used for the analyses are summarized in Table 3.12. A total of 471 patients were randomized into the study (APRS) and a total of 469 patients received double-blind study product and comprised the all-patient-treated set (APTS). The remaining 2 randomized patients withdrew their consent to participate before taking any double-blind study product; thus, these patients were not included in the APTS.

When sufficient numbers of patients had been screened, the recruitment was stopped; however, at several centers a number of patients were already scheduled for screening visits, thus partly accounting for the higher recruitment than anticipated; these patients were included for ethical reasons.

Table 3.12. Summary of Patient Disposition in All-Patient-Randomized Set for Study 99003

	Placebo n (%)	Citalopram n (%)	Escitalopram n (%)	Total n (%)
Patients Randomized	154	161	156	471
Patients Treated	154	160	155	469
Patients Completed	139 (90.3)	152 (95.0)	146 (94.2)	437 (93.2)
Patients Withdrawn from APTS	15 (9.7)	8 (5.0)	9 (5.8)	32 (6.8)
Patient Data Sets:				
All Patients Treated Set (APTS)	154	160	155	469
Full Analysis Set (FAS)	154	159	155	468
Per Protocol Set (PPS)	144	151	146	441

The reasons of patient withdrawal are summarized in Table 3.13. The most common reasons for withdrawal were adverse events (AEs) and lack of efficacy. Five patients in the placebo group withdrew due to lack of efficacy as the primary reason compared to 0 patients in the escitalopram and 1 patient in the citalopram group. The number of patients who withdrew due to an AE was similar between the different treatment groups.

Table 3.13 Withdrawals from Study by Primary Reason in the All-Patient-Treated Set for Study 99003

	Treatment Groups						Total	
	PBO		CIT		ESC		n	(%)
	n	(%)	n	(%)	n	(%)	n	(%)
Patients Treated	154		160		155		469	
Patients Withdrawn	15	( 9.7)	8	( 5.0)	9	( 5.8)	32	( 6.8)
Primary Reason:								
Adverse Event(s)	4	( 2.6)	6	( 3.8)	4	( 2.6)	14	( 3.0)
Lack of efficacy	5	( 3.2)	1	( 0.6)	0	( 0.0)	6	( 1.3)
Non-compliance with study medication	0	( 0.0)	0	( 0.0)	0	( 0.0)	0	( 0.0)
Protocol violation	1	( 0.6)	0	( 0.0)	2	( 1.3)	3	( 0.6)
Withdrawal of consent	1	( 0.6)	0	( 0.0)	1	( 0.6)	2	( 0.4)
Lost to follow up	2	( 1.3)	1	( 0.6)	2	( 1.3)	5	( 1.1)
Administrative	0	( 0.0)	0	( 0.0)	0	( 0.0)	0	( 0.0)
Other reason(s)	2	( 1.3)	0	( 0.0)	0	( 0.0)	2	( 0.4)

### 3.1.4.2 Baseline Comparability of Treatment Groups

The patient demographic values at baseline are summarized in Table 3.14. The demographic values were similar for the escitalopram, citalopram and placebo groups. In the study, there was an approximate 3 to 1 ratio of women to men, and almost all patients were Caucasian. There were no statistically significant imbalance in age or sex between treatment groups.

Table 3.14 Summary of Patient Demographics in All-Patient-Treated Set for Study 99003

		Treatment Groups							
		PBO		CIT		ESC		Total	
		stats	(%)	stats	(%)	stats	(%)	stats	(%)
Patients Treated	n	154		160		155		469	
Sex	Male	43	(27.9)	49	(30.6)	39	(25.2)	131	(27.9)
	Female	111	(72.1)	111	(69.4)	116	(74.8)	338	(72.1)
Age (yrs.)	n	154		160		155		469	
	Mean	43		44		43		43	
	Median	43		45		43		44	
	SD	12		11		11		11	
	Min.	18		19		20		18	
	Max.	65		65		65		65	
Race	Caucasian	154	(100.)	156	(97.5)	153	(98.7)	463	(98.7)
	Black	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Asian	0	(0.0)	2	(1.3)	2	(1.3)	4	(0.9)
	Other	0	(0.0)	2	(1.3)	0	(0.0)	2	(0.4)

For baseline efficacy parameters, at baseline, approximately 90% of patients were moderately ill (MADRS total score from 22 to 34) and approximately 10% of patients were severely ill (MADRS total score  $\geq 35$ , although no patients had a MADRS total score  $>40$  in this study). The mean MADRS total score was approximately 29 for each treatment group and the mean CGI-S score was approximately 4.3 for each treatment group. The treatment groups were judged to be clinically similar at baseline and there were no statistically significant differences between treatment groups.

### 3.1.4.3 Efficacy Evaluation

All efficacy analyses were conducted on the full-analysis set. No efficacy analyses were conducted on the per-protocol set, since the number of patients in this set did not differ from that in the full-analysis set by more than 10%, which was less than the 20% specified in the SAP.

#### 3.1.4.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint was defined as the change in the MADRS total score from baseline to last assessment using LOCF and applying the Week 8 visit window\*. What the sponsor did was if the data were available on Week 8 visit window, then the one which is closer to Day 56 was chosen as the last observation, otherwise the last observation was used although it may not be the evaluable one in its specific window. (It is called LOCF in this review). Escitalopram was statistically significantly superior to placebo with an estimated difference in change of MADRS total score 2.9 points greater than that for the placebo. Tables 3.15 and 3.16 show the adjusted mean change in MADRS total scores from baseline for each treatment group at Endpoint by LOCF and

\* The sponsor pre-specified a table of time window for each scheduled visit in the Statistical Analysis Plan. The Week 8 visit window was defined from Days 50 to 63, but in SAP it says that 'The upper limit of the week 8 window may be extended to accommodate all data from that visit.'

the difference between individual drug treatment group versus the placebo, respectively. As we can observe from the tables, the escitalopram group had the greatest improvement over the course of the study, followed by the citalopram group, with the placebo group showing the least improvement. Escitalopram was statistically significantly superior to placebo with an estimated difference in change of MADRS total score 2.9 points greater than that for placebo ( $p=0.002$ ). This constitutes the result of the primary efficacy analysis.

Citalopram was also numerically superior to placebo with an estimated difference in change of MADRS total score 1.5 points greater than that for placebo, although the difference was not statistically significant.

Table 3.15 Adjusted Mean Change from Baseline in MADRS Total Scores at the Primary Endpoint for Study 99003

Treatment Group	n	Least Squares Mean	SE	95% Confidence Limits	
				Lower	Upper
PBO	154	-12.11	0.67	-13.44	-10.78
CIT	159	-13.59	0.67	-14.91	-12.27
ESC	155	-15.02	0.67	-16.35	-13.69

Table 3.16 Treatment Difference of the Adjusted Mean Changes from Baseline in MADRS Total Score at Primary Endpoint for Study 99003

Treatment Difference	Least Squares Mean	SE	95% Confidence Limits		p-value
			Lower	Upper	
CIT-PBO	-1.48	0.92	-3.30	0.33	0.109
ESC-PBO	-2.91	0.93	-4.73	-1.09	0.002

Some statistical aspects about the primary efficacy analysis are summarized as follows.

### Centers

Using the grouping rule described in SAP, the following centers were merged into a single collective center and coded as 9999: 1001, 1106, 1110, 1115, 1133, 1506, 1601, 1704, 1802, 1807, and 1810. Center 1606 (Switzerland) only screened 1 patient, who was not randomized into the study. Thus, this center was not relevant for the efficacy analysis. This resulted in a total of 58 centers.

There was no statistically significant treatment-by-center interaction; however, there was a statistically significant center effect with  $p<0.0001$ . This means that centers did behave differently, but the differences were independent of the treatment given.

## Residuals and Test for Normality

Various checks of the model were performed. Although the calculated standardized residuals showed no systematic trends on a scatter plot against predicted values, the histogram of residuals showed tendencies of a skewed distribution, and the test for normality was rejected ( $p=0.0036$ ). The robustness of the chosen ANCOVA method against departures from normality, however, was confirmed by additional analyses using ranks, non-parametric statistics, and transforming MADRS scores with the square root.

### *3.1.4.3.2 Secondary Efficacy Endpoints*

#### MADRS Adjusted Total Scores Per Visit

Table 6.8 in the appendices and Table 3.17 show the least square mean of MADRS total scores at each visit by OC and the endpoint by LOCF analyses for each treatment group and, the differences between individual drug groups and the placebo, respectively. As we can observe from the tables, the mean changes of MADRS total scores from baseline in both active treatment groups are larger than in the placebo group throughout the study. Moreover, escitalopram was statistically significantly superior to placebo at all visits for the estimated difference in adjusted mean change in MADRS total score including the last visit, which represents the primary efficacy endpoint. For the comparisons between citalopram group and the placebo, the citalopram group was numerically superior to the placebo group at all visits for the estimated mean change in MADRS total score but the differences were not statistically significant. When using LOCF at each visit a statistically significant difference between escitalopram and placebo was seen from Week 2 and onward, so the sponsor also concluded that the similarity of the OC and LOCF analyses indicated the robustness of the model in this study.

Table 3.17 Treatment Difference of the Adjusted Mean Changes from Baseline in MADRS Total Score for Study 99003

Treatment Difference	Visit #		Least Squares Mean	SE	95% Confidence Limits		p-value
					Lower	Upper	
CIT-PBO	Week 1	(OC)	-0.79	0.56	-1.89	0.31	0.160
	Week 2	(OC)	-0.71	0.69	-2.06	0.64	0.304
	Week 3	(OC)	-0.90	0.81	-2.49	0.68	0.264
	Week 4	(OC)	-1.44	0.86	-3.13	0.25	0.095
	Week 6	(OC)	-1.40	0.86	-3.10	0.30	0.105
	Week 8	(OC)	-1.01	0.88	-2.75	0.73	0.252
	Last	(LOCF)	-1.48	0.92	-3.30	0.33	0.109
ESC-PBO	Week 1	(OC)	-1.27	0.56	-2.37	-0.17	0.023
	Week 2	(OC)	-1.44	0.69	-2.80	-0.09	0.037
	Week 3	(OC)	-1.79	0.82	-3.39	-0.18	0.029
	Week 4	(OC)	-2.77	0.87	-4.48	-1.06	0.002
	Week 6	(OC)	-2.56	0.87	-4.27	-0.85	0.003
	Week 8	(OC)	-2.35	0.89	-4.11	-0.59	0.009
	Last	(LOCF)	-2.91	0.93	-4.73	-1.09	0.002

#### Proportion of Patients with a $\geq 50\%$ Reduction in MADRS Total Score (Responders)

The proportion of patients with at least a 50% reduction of the baseline MADRS total score (responders) for each treatment group by visit (OC) and last assessment (LOCF) is

shown in Table 6.9 of the appendices. The differences between both drug groups and the placebo are shown in Table 3.18. As we can observe from the tables, the difference in the proportion between escitalopram-treated and placebo-treated patients was statistically significantly ( $p \leq 0.05$ , Fisher's exact test) in favor of escitalopram at Weeks 6 and 8 (OC), and the last visit (LOCF).

Table 3.18 Differences between Treatment Groups in the Proportion of Patients with  $\geq 50\%$  Reduction in MADRS Total Score for Study 99003

Treatment Difference	Visit #		MADRS $\geq 50\%$ Reduction Resp.rate Dif. (%)	95% Confidence Limits		p-value
				Lower(%)	Upper(%)	
CIT-PBO	Week 1	(OC)	-0.8	-5.4	3.8	0.783
	Week 2	(OC)	-1.6	-9.5	6.3	0.732
	Week 3	(OC)	-5.4	-15.7	5.0	0.364
	Week 4	(OC)	2.0	-8.5	12.4	0.802
	Week 6	(OC)	5.3	-5.9	16.5	0.404
	Week 8	(OC)	4.2	-7.4	15.7	0.555
	Last	(LOCF)	6.2	-4.9	17.2	0.308
	ESC-PBO	Week 1	(OC)	0.5	-4.4	5.4
Week 2		(OC)	3.5	-5.0	12.0	0.427
Week 3		(OC)	-4.6	-15.2	5.9	0.433
Week 4		(OC)	10.8	-0.1	21.8	0.065
Week 6		(OC)	12.8	1.4	24.1	0.033
Week 8		(OC)	15.6	4.2	27.1	0.009
Last		(LOCF)	17.8	6.8	28.7	0.002

#### Proportion of Patients in Complete Remission (MADRS Score $\leq 12$ )

The proportion of patients in complete remission (MADRS score  $\leq 12$ ) in each treatment group by visit is shown in Table 6.10 of the appendices and the differences between treatment groups in the proportion of patients in remission are shown in Table 3.19. This difference was statistically significant in favor of escitalopram at Week 6 using either OC or LOCF (Note: the by visit LOCF results are not shown in this review).

Table 3.19 Differences between Treatment Groups in the Proportion of Patients with MADRS Scores  $\leq 12$  for Study 99003

Treatment Difference	Visit #		MADRS $\leq 12$ Resp.rate Dif. (%)	95% Confidence Limits		p-value
				Lower(%)	Upper(%)	
CIT-PBO	Week 1	(OC)	1.3	-1.9	4.4	0.685
	Week 2	(OC)	-4.2	-11.3	3.0	0.261
	Week 3	(OC)	-2.1	-11.5	7.2	0.668
	Week 4	(OC)	0.3	-9.7	10.2	1.000
	Week 6	(OC)	4.8	-5.9	15.5	0.384
	Week 8	(OC)	-3.6	-15.0	7.9	0.553
	Last	(LOCF)	-1.3	-12.2	9.6	0.819
	ESC-PBO	Week 1	(OC)	0.6	-2.3	3.5
Week 2		(OC)	-1.9	-9.4	5.6	0.716
Week 3		(OC)	0.4	-9.3	10.1	1.000
Week 4		(OC)	4.0	-6.3	14.3	0.511
Week 6		(OC)	12.0	1.1	23.0	0.037
Week 8		(OC)	6.8	-4.8	18.4	0.285
Last		(LOCF)	9.4	-1.6	20.5	0.110

### CGI-Severity Scores (Analyzed by ANCOVA)

The adjusted mean CGI-S scores from baseline for each treatment group by visit (OC) and last visit (LOCF) is shown in Table 6.11 of the appendices and the comparisons between both drug groups and the placebo by visit are shown in Table 3.20.

Table 3.20 Treatment Difference of the Adjusted Mean Changes from Baseline in CGI Severity Score for Study 99003

Treatment Difference	Visit #		Least Squares Mean	SE	95% Confidence Limits		p-value
					Lower	Upper	
CIT-PBO	Week 1	(OC)	-0.07	0.08	-0.22	0.09	0.403
	Week 2	(OC)	-0.03	0.10	-0.23	0.16	0.729
	Week 3	(OC)	-0.17	0.12	-0.40	0.06	0.143
	Week 4	(OC)	-0.17	0.12	-0.41	0.07	0.172
	Week 6	(OC)	-0.12	0.13	-0.37	0.13	0.346
	Week 8	(OC)	-0.13	0.13	-0.39	0.12	0.303
	Last	(LOCF)	-0.15	0.13	-0.40	0.10	0.245
	ESC-PBO	Week 1	(OC)	-0.16	0.08	-0.32	-0.01
Week 2		(OC)	-0.22	0.10	-0.41	-0.02	0.032
Week 3		(OC)	-0.34	0.12	-0.57	-0.11	0.004
Week 4		(OC)	-0.31	0.13	-0.56	-0.06	0.016
Week 6		(OC)	-0.23	0.13	-0.49	0.02	0.072
Week 8		(OC)	-0.35	0.13	-0.60	-0.09	0.008
Last		(LOCF)	-0.38	0.13	-0.64	-0.13	0.003

Throughout the study the escitalopram group showed more improvement than the placebo group. Escitalopram was statistically significantly superior to placebo from Week 1 (OC) onwards, with the exception of Week 6 which only showed statistically significant differences at the 10% level. Citalopram was only numerically superior to placebo at all visits for OC analyses and Week 4 for LOCF analyses (Note: The by visit LOCF analyses results are not shown in this review).

### Cochran-Mantel-Haenszel Analysis of CGI-S Score at Week 8 (LOCF)

A non-parametric Cochran-Mantel-Haenszel (CMH) test, with individual centers comprising the strata, showed an overall statistical difference among treatment groups mean CGI-S scores ( $p=0.043$ ). Pairwise comparisons of treatment groups using the CMH test, showed escitalopram to be statistically significantly superior to placebo ( $p=0.0138$ ), while there were no statistical difference between citalopram and placebo.

### Proportion of Patients with CGI-Severity Scores of 1 or 2

The proportion of patients with a CGI-S score of 1 (normal, not at all ill) or 2 (borderline ill) by treatment group and visit is shown in Table 6.12 of the appendices. The differences between individual treatment groups versus the placebo are shown in Table 3.21. As we can observe from the tables, a greater percentage of patients in the escitalopram group had CGI-S scores of 1 or 2 from Week 2 onwards compared to patients in the placebo or citalopram groups. Moreover, escitalopram was statistically significantly superior to placebo at the last visit by LOCF by Chi-Square test. ( $p=0.053$  by Fisher's exact test and  $p=0.046$  by  $\chi^2$ ).

Table 3.21 Differences between Treatment Groups in the Proportion of Patients with CGI Severity Scores of 1 or 2 for Study 99003

Treatment Difference	Visit @		CGI-S 1 or 2* Resp.rate Dif. (%)	95% Confidence Limits		p-value
				Lower(%)	Upper(%)	
CIT-PBO	Week 1	(OC)	-2.2	-6.5	2.1	0.369
	Week 2	(OC)	-3.4	-10.9	4.1	0.391
	Week 3	(OC)	1.2	-8.3	10.7	0.889
	Week 4	(OC)	5.1	-5.4	15.6	0.358
	Week 6	(OC)	1.7	-9.5	12.8	0.808
	Week 8	(OC)	2.7	-9.0	14.3	0.720
	Last	(LOCF)	5.6	-5.4	16.6	0.363
ESC-PBO	Week 1	(OC)	-0.2	-5.0	4.6	1.000
	Week 2	(OC)	2.6	-5.7	10.9	0.630
	Week 3	(OC)	8.5	-1.5	18.5	0.110
	Week 4	(OC)	5.9	-4.7	16.6	0.289
	Week 6	(OC)	5.5	-6.0	16.9	0.392
	Week 8	(OC)	10.5	-1.3	22.2	0.093
	Last	(LOCF)	11.3	0.3	22.4	0.053

CGI-Improvement Scores (Analyzed by the ANCOVA)

The adjusted mean of CGI-I scores for each treatment group by visit (OC) and last visit (LOCF) are shown in Table 6.13 and the least squares estimates for between-group differences are shown in Table 3.22. As we can observe from the tables, the escitalopram group was statistically significantly superior to the placebo group at all visits during the study for the estimated difference in adjusted mean CGI-I score. The citalopram group was numerically superior to placebo at all visits, but only statistically significantly superior at Week 8 (OC) and the last visit (LOCF).

Table 3.22 Treatment Difference in the Adjusted Means of CGI Improvement Scores for Study 99003

Treatment Difference	Visit @		Least Squares Mean	SE	95% Confidence Limits		p-value
					Lower	Upper	
CIT-PBO	Week 1	(OC)	-0.14	0.11	-0.35	0.08	0.221
	Week 2	(OC)	-0.05	0.12	-0.28	0.19	0.695
	Week 3	(OC)	-0.14	0.12	-0.39	0.10	0.249
	Week 4	(OC)	-0.22	0.13	-0.47	0.04	0.092
	Week 6	(OC)	-0.20	0.12	-0.44	0.04	0.100
	Week 8	(OC)	-0.26	0.12	-0.50	-0.03	0.025
	Last	(LOCF)	-0.31	0.12	-0.55	-0.06	0.014
ESC-PBO	Week 1	(OC)	-0.24	0.11	-0.45	-0.02	0.033
	Week 2	(OC)	-0.27	0.12	-0.51	-0.04	0.023
	Week 3	(OC)	-0.34	0.13	-0.59	-0.09	0.008
	Week 4	(OC)	-0.44	0.13	-0.70	-0.18	0.001
	Week 6	(OC)	-0.29	0.12	-0.53	-0.05	0.016
	Week 8	(OC)	-0.35	0.12	-0.59	-0.12	0.003
	Last	(LOCF)	-0.43	0.12	-0.67	-0.18	0.001

### Cochran-Mantel-Haenszel Analysis of CGI-I Score at Week 8 by LOCF

A non-parametric Cochran-Mantel-Haenszel test, with individual centers comprising the strata, showed overall statistical differences among treatment group mean CGI-I scores ( $p = 0.0029$ ). Pairwise comparisons of treatment groups, using the CMH test showed both escitalopram and citalopram to be statistically significantly superior to placebo ( $p = 0.0017$  and  $p = 0.0089$ , respectively).

### Proportion of Patients with CGI-Improvement Scores of 1 or 2

The proportions of patients with a CGI-I score of 1 (very much improved) or 2 (much improved) for individual treatment groups by visit are shown in Table 6.14 of appendices. In general, a greater percentage of patients in the escitalopram group had CGI-I scores of 1 or 2 from Week 1 onward compared to patients in the placebo or citalopram groups.

The differences between treatment groups for citalopram versus placebo and escitalopram versus placebo are shown in Table 3.23. As we can observe from the table, the escitalopram group was statistically significantly superior to the placebo group from Week 3 onwards.

Table 3.23 Differences between Treatment Groups in the Proportion of Patients with CGI Improvement Scores of 1 or 2 for Study 99003

Treatment Difference	Visit #		CGI-I 1 or 2* Resp.rate Dif. (%)	95% Confidence Limits		p-value
				Lower(%)	Upper(%)	
CIT-PBO	Week 1	(OC)	4.9	-3.3	13.1	0.273
	Week 2	(OC)	-4.3	-14.7	6.2	0.441
	Week 3	(OC)	8.7	-2.6	20.0	0.156
	Week 4	(OC)	8.5	-2.8	19.7	0.161
	Week 6	(OC)	10.5	-0.9	21.8	0.078
	Week 8	(OC)	7.9	-3.2	18.9	0.177
	Last	(LOCF)	10.2	-0.6	21.0	0.067
ESC-PBO	Week 1	(OC)	6.7	-1.7	15.1	0.127
	Week 2	(OC)	11.0	-0.1	22.1	0.066
	Week 3	(OC)	14.1	2.7	25.6	0.018
	Week 4	(OC)	17.0	5.6	28.3	0.005
	Week 6	(OC)	12.8	1.5	24.2	0.033
	Week 8	(OC)	15.7	5.0	26.5	0.005
	Last	(LOCF)	18.4	7.8	28.9	0.001

#### 3.1.4.4 Sponsor's Efficacy Conclusions

The primary efficacy analysis showed a statistically significantly superior therapeutic effect for escitalopram compared to placebo. The analysis showed a change in MADRS total score from baseline to Week 8 (LOCF) of 15.0 points in the escitalopram group and 12.1 points in the placebo group with a difference of 2.9 points in favor of escitalopram.

In support of the primary analysis, escitalopram was statistically superior to placebo from Week 2 onwards (LOCF) and at all visits (OC) in the secondary analysis of the change in MADRS total score from baseline to each visit. The proportion of

escitalopram responders, defined as a reduction of  $\geq 50\%$  on the MADRS total score, was statistically superior to that of placebo responders from Week 4 onwards (LOCF) and at Weeks 6 and 8 (OC). The proportion of escitalopram-treated patients in complete remission, defined as a MADRS total score  $\leq 12$ , was only numerically superior to that of placebo-treated patients at the last visit (LOCF).

Escitalopram was statistically superior to the placebo on analyses of CGI-I from Week 2 onwards (LOCF) and all assessments (OC). The proportion of very much or much improved patients on the CGI-I scale was statistically superior in the escitalopram group compared with the placebo group from Week 3 onwards (OC and LOCF). Furthermore, escitalopram was statistically superior to placebo on the CGI-S scale from Week 1 (OC) and Week 2 (LOCF) onwards, with the exception of Week 6 which only showed statistically significant differences at the 10% level; and the proportion of escitalopram-treated patients who had scores of 1 or 2 on the CGI-S scale was statistically superior at the last visit (LOCF) and only numerically superior to that of placebo at all visits (OC).

About citalopram, based on the adjusted values, it was numerically superior to placebo on the mean MADRS total score, the mean CGI-S score, and the mean CGI-I score throughout the study. Especially, citalopram was statistically superior to placebo on the CGI-I at the last visit (LOCF) and at Week 8 (OC).

#### **3.1.4.5 Statistical Reviewer's Findings and Comments**

1. This reviewer confirmed the sponsor's analysis results for all efficacy endpoints for all visits by both observed case analysis and LOCF analysis. However, since the sponsor did not simply use the last available evaluable visit observations to impute the missing observations for all missing visits, [instead, they used a rule (see Section 3.1.4.3.1) to choose a best fit observation to impute the missing observation for each patient], their analysis results were different from the reviewer's LOCF analysis results. Nevertheless, this reviewer found that the differences were not large enough to affect the final conclusions. In conclusion, this reviewer agrees with the sponsor that the data from this study support the escitalopram's efficacy.

#### **3.2 Evaluation of Safety**

The evaluation of safety was not performed in this review.

### **4 Findings in Special/Subgroup Populations**

The sponsor did not include any subgroup analysis results in their original sNDA submission. Although they were later asked to do so, the sponsor only performed the subgroup analysis by the combined study data. So, in this section this reviewer reports her analysis results for individual studies by using the same model to analyze the primary endpoint.

#### 4.1 Gender

Tables 4.1 and 4.2 show this reviewer's subgroup analysis results for gender for the primary endpoint, change from baseline to Week 8 by LOCF on the MADRS Total scores for Studies 99001 and 99003, respectively. As we can observe from the tables, for both studies, the escitalopram is still significantly better than the placebo for female patients which occupy the larger proportion of total patients.

Table 4.1 Subgroup Analysis Results for Gender on the MADRS Total Scores for Study 99001

Variable	Visit	Least Square Means	SE	P-value
Male				
PBO (n=42)	Last (LOCF)	-14.57	1.40	
ESC (n=50)	Last (LOCF)	-15.44	1.46	
ESC-PBO	Last (LOCF)	-0.87	1.79	0.6282
Female				
PBO (n=147)	Last (LOCF)	-13.34	0.81	
ESC (n=138)	Last (LOCF)	-16.36	0.82	
ESC-PBO	Last (LOCF)	-3.02	0.99	0.0025

Table 4.2 Subgroup Analysis Results for Gender on the MADRS Total Scores for Study 99003

Variable	Visit	Least Square Means	SE	P-value
Male				
PBO (n=43)	Last (LOCF)	-11.04	1.63	
CIT (n=49)	Last (LOCF)	-13.39	1.47	
ESC (n=39)	Last (LOCF)	-14.45	1.70	
CIT-PBO	Last (LOCF)	-2.345	2.24	0.2975
ESC-PBO	Last (LOCF)	-3.41	2.36	0.1524
Female				
PBO (n=111)	Last (LOCF)	-12.05	0.81	
CIT (n=110)	Last (LOCF)	-14.21	0.82	
ESC (n=116)	Last (LOCF)	-15.61	0.79	
CIT-PBO	Last (LOCF)	-2.16	1.13	0.057
ESC-PBO	Last (LOCF)	-3.56	1.11	0.001

#### 4.2 Race

The subgroup analyses for race was not performed due to the majority of patients were white.

#### 4.3 Age

This reviewer performed the subgroup analysis for age categorized by 50 years old. Tables 4.3 and 4.4 show the results. It was noticed that for Study 99003, the placebo had better performance than escitalopram in the older patient (>50) group.

Table 4.3 Subgroup Analysis Results for Age on the MADRS Total Scores for Study 99001

Variable	Visit	Least Square Means	SE	P-value
Age ≤ 50				
PBO (n=146)	Last (LOCF)	-13.90	0.83	
ESC (n=148)	Last (LOCF)	-16.69	0.80	
ESC-PBO	Last (LOCF)	-2.79	0.97	0.005
Age >50				
PBO (n=43)	Last (LOCF)	-12.23	1.58	
ESC (n=40)	Last (LOCF)	-14.84	1.81	
ESC-PBO	Last (LOCF)	-2.61	2.23	0.2481

Table 4.4 Subgroup Analysis Results for Age on the MADRS Total Scores for Study 99003

Variable	Visit	Least Square Means	SE	P-value
Age ≤ 50				
PBO (n=106)	Last (LOCF)	-11.80	0.86	
CIT (n=107)	Last (LOCF)	-13.26	0.86	
ESC (n=111)	Last (LOCF)	-15.60	0.83	
CIT-PBO	Last (LOCF)	-1.47	1.16	0.207
ESC-PBO	Last (LOCF)	-3.81	1.14	0.001
Age >50				
PBO (n=48)	Last (LOCF)	-13.57	1.24	
CIT (n=52)	Last (LOCF)	-13.68	1.22	
ESC (n=44)	Last (LOCF)	-12.41	1.27	
CIT-PBO	Last (LOCF)	-0.11	1.72	0.951
ESC-PBO	Last (LOCF)	1.17	1.76	0.508

#### 4.4 Other Special/Subgroup Populations

There is no special/subgroup population subgroup analysis performed for this submission.

## 5 Summary and Conclusions

### 5.1 Statistical Issues and Collective Evidence

This reviewer confirmed the sponsor's analysis results for all efficacy endpoints for all visits for both the observed case and LOCF analyses. Since the sponsor did not simply use the last available evaluable observed visit values to impute the missing values at the last visit, (instead they used a rule to choose most suitable observations to impute the missing values) their analysis results were different from this reviewer's LOCF analysis results. These differences were, however, not large enough to affect the final conclusions. In conclusion, this reviewer agrees with the sponsor that the data support the escitalopram's efficacy for both studies.

## **5.2 Conclusions and Recommendations**

After carefully evaluating the sponsor's submission and analysis results, this reviewer agrees with the sponsor that for both studies the data support the escitalopram's efficacy.

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Mathematical Statistician

Concurrence:

Dr. Jin

Dr. Mahjoob

cc: NDA 21-323/SE8-007 & 21-365/SE8-001

HFD-120/Dr. Katz

HFD-120/Dr. Laughren

HFD-120/Dr. Alfaro

HFD-120/Mr. David

HFD-700/Dr. Anello

HFD-710/Dr. Chi

HFD-710/Dr. Mahjoob

HFD-710/Dr. Jin

HFD-710/Dr. Chen

This review consists of 37 pages. MS Word: C:/yfchen/NDA21323/review.doc

## 6 Appendices

Table 6.1 Adjusted Mean Change from Baseline in MADRS Total Score for Study 99001

Treatment Group	Visit #		n	Least Squares Mean	SE	95% Confidence Limits	
						Lower	Upper
PBO	Week 1	(OC)	185	-4.26	0.41	-5.06	-3.46
	Week 2	(OC)	174	-6.86	0.52	-7.90	-5.83
	Week 3	(OC)	172	-9.75	0.59	-10.91	-8.59
	Week 4	(OC)	169	-12.09	0.60	-13.28	-10.91
	Week 6	(OC)	162	-12.79	0.68	-14.13	-11.45
	Week 8	(OC)	159	-14.72	0.64	-16.00	-13.45
	Last	(LOCF)	189	-13.60	0.69	-14.96	-12.24
ESC	Week 1	(OC)	186	-4.99	0.40	-5.78	-4.20
	Week 2	(OC)	180	-8.73	0.52	-9.76	-7.70
	Week 3	(OC)	173	-12.52	0.59	-13.69	-11.35
	Week 4	(OC)	171	-14.56	0.60	-15.75	-13.37
	Week 6	(OC)	166	-16.43	0.68	-17.77	-15.09
	Week 8	(OC)	161	-17.42	0.64	-18.69	-16.15
	Last	(LOCF)	188	-16.27	0.69	-17.63	-14.92

Table 6.2 Proportion of Patients with  $\geq 50\%$  Reduction in MADRS Total Score by Week for Study 99001

Treatment Group	Visit #		n	MADRS $\geq 50\%$ reduction		95% Confidence Limits	
				n	%	Lower(%)	Upper(%)
PBO	Week 1	(OC)	185	7	3.8	1.5	7.6
	Week 2	(OC)	174	25	14.4	9.5	20.5
	Week 3	(OC)	172	50	29.1	22.4	36.5
	Week 4	(OC)	169	62	36.7	29.4	44.4
	Week 6	(OC)	162	66	40.7	33.1	48.7
	Week 8	(OC)	159	76	47.8	39.8	55.9
	Last	(LOCF)	189	79	41.8	34.7	49.2
ESC	Week 1	(OC)	186	12	6.5	3.4	11.0
	Week 2	(OC)	180	29	16.1	11.1	22.3
	Week 3	(OC)	173	63	36.4	29.2	44.1
	Week 4	(OC)	171	81	47.4	39.7	55.1
	Week 6	(OC)	166	96	57.8	49.9	65.4
	Week 8	(OC)	161	100	62.1	54.1	69.6
	Last	(LOCF)	188	104	55.3	47.9	62.6

Table 6.3 Proportion of Patients with MADRS Total Score ≤ 12 for Study 99001

Treatment Group	Visit #	n	MADRS ≤ 12		95% Confidence Limits	
			n	%	Lower(%)	Upper(%)
PBO	Week 1 (OC)	185	4	2.2	0.6	5.4
	Week 2 (OC)	174	14	8.0	4.5	13.1
	Week 3 (OC)	172	37	21.5	15.6	28.4
	Week 4 (OC)	169	48	28.4	21.7	35.8
	Week 6 (OC)	162	54	33.3	26.1	41.2
	Week 8 (OC)	159	61	38.4	30.8	46.4
	Last (LOCF)	189	64	33.9	27.2	41.1
	ESC	Week 1 (OC)	186	9	4.8	2.2
Week 2 (OC)		180	24	13.3	8.7	19.2
Week 3 (OC)		173	44	25.4	19.1	32.6
Week 4 (OC)		171	63	36.8	29.6	44.5
Week 6 (OC)		166	82	49.4	41.6	57.3
Week 8 (OC)		161	85	52.8	44.8	60.7
Last (LOCF)		188	89	47.3	40.0	54.7

Table 6.4 Adjusted Mean Change from Baseline in CGI Severity Scores for Study 99001

Treatment Group	Visit #	n	Least Squares Mean	SE	95% Confidence Limits	
					Lower	Upper
PBO	Week 1 (OC)	184	-0.44	0.05	-0.54	-0.34
	Week 2 (OC)	174	-0.72	0.07	-0.85	-0.58
	Week 3 (OC)	172	-1.14	0.08	-1.30	-0.98
	Week 4 (OC)	168	-1.38	0.09	-1.56	-1.20
	Week 6 (OC)	162	-1.56	0.10	-1.75	-1.36
	Week 8 (OC)	158	-1.80	0.10	-1.99	-1.60
	Last (LOCF)	189	-1.63	0.10	-1.82	-1.44
	ESC	Week 1 (OC)	186	-0.42	0.05	-0.52
Week 2 (OC)		180	-0.87	0.07	-1.01	-0.74
Week 3 (OC)		173	-1.45	0.08	-1.62	-1.28
Week 4 (OC)		171	-1.67	0.09	-1.85	-1.48
Week 6 (OC)		165	-1.89	0.10	-2.09	-1.69
Week 8 (OC)		160	-2.05	0.10	-2.25	-1.85
Last (LOCF)		188	-1.86	0.10	-2.05	-1.66

Table 6.5 Proportion of Patients with CGI Severity Scores of 1 or 2 for Study 99001

Treatment Group	Visit #	n	CGI-S 1 or 2*		95% Confidence Limits	
			n	%	Lower(%)	Upper(%)
PBO	Week 1 (OC)	184	6	3.3	1.2	7.0
	Week 2 (OC)	174	13	7.5	4.0	12.4
	Week 3 (OC)	172	39	22.7	16.6	29.7
	Week 4 (OC)	168	51	30.4	23.5	37.9
	Week 6 (OC)	162	63	38.9	31.3	46.9
	Week 8 (OC)	158	69	43.7	35.8	51.8
	Last (LOCF)	189	70	37.0	30.1	44.3
	ESC	Week 1 (OC)	186	4	2.2	0.6
Week 2 (OC)		180	16	8.9	5.2	14.0
Week 3 (OC)		173	45	26.0	19.6	33.2
Week 4 (OC)		171	68	39.8	32.4	47.5
Week 6 (OC)		165	76	46.1	38.3	54.0
Week 8 (OC)		160	79	49.4	41.4	57.4
Last (LOCF)		188	82	43.6	36.4	51.0

Table 6.6 Adjusted Mean CGI Improvement Score for Study 99001

Treatment Group	Visit #		n	Least Squares Mean	SE	95% Confidence Limits	
						Lower	Upper
PBO	Week 1	(OC)	184	3.37	0.07	3.23	3.51
	Week 2	(OC)	174	3.02	0.08	2.87	3.17
	Week 3	(OC)	172	2.71	0.08	2.55	2.88
	Week 4	(OC)	168	2.42	0.08	2.26	2.59
	Week 6	(OC)	162	2.43	0.10	2.24	2.63
	Week 8	(OC)	158	2.24	0.09	2.06	2.42
	Last	(LOCF)	189	2.39	0.10	2.20	2.58
	ESC	Week 1	(OC)	186	3.18	0.07	3.04
Week 2		(OC)	180	2.81	0.08	2.66	2.96
Week 3		(OC)	173	2.30	0.08	2.14	2.46
Week 4		(OC)	171	2.20	0.08	2.03	2.37
Week 6		(OC)	165	2.03	0.10	1.84	2.23
Week 8		(OC)	160	1.91	0.09	1.74	2.09
Last		(LOCF)	188	2.06	0.10	1.87	2.25

Table 6.7 Proportion of Patients with CGI Improvement Scores of 1 or 2 for Study 99001

Treatment Group	Visit #		n	CGI-I 1 or 2*		95% Confidence Limits	
				n	%	Lower	Upper
PBO	Week 1	(OC)	184	23	12.5	8.1	18.2
	Week 2	(OC)	174	50	28.7	22.1	36.1
	Week 3	(OC)	172	77	44.8	37.2	52.5
	Week 4	(OC)	168	96	57.1	49.3	64.7
	Week 6	(OC)	162	86	53.1	45.1	61.0
	Week 8	(OC)	158	96	60.8	52.7	68.4
	Last	(LOCF)	189	100	52.9	45.5	60.2
	ESC	Week 1	(OC)	186	35	18.8	13.5
Week 2		(OC)	180	66	36.7	29.6	44.2
Week 3		(OC)	173	98	56.6	48.9	64.1
Week 4		(OC)	171	108	63.2	55.5	70.4
Week 6		(OC)	165	114	69.1	61.4	76.0
Week 8		(OC)	160	115	71.9	64.2	78.7
Last		(LOCF)	188	123	65.4	58.2	72.2

Table 6.8 Adjusted Mean Change from Baseline in MADRS Total Scores for Study 99003

Treatment Group	Visit #		n	Least Squares Mean	SE	95% Confidence Limits	
						Lower	Upper
PBO	Week 1	(OC)	149	-3.13	0.41	-3.94	-2.33
	Week 2	(OC)	140	-6.76	0.51	-7.76	-5.75
	Week 3	(OC)	141	-8.84	0.59	-10.01	-7.66
	Week 4	(OC)	144	-9.06	0.63	-10.31	-7.81
	Week 6	(OC)	145	-11.18	0.63	-12.43	-9.94
	Week 8	(OC)	138	-13.54	0.66	-14.84	-12.24
	Last	(LOCF)	154	-12.11	0.67	-13.44	-10.78
GIT	Week 1	(OC)	154	-3.92	0.40	-4.72	-3.12
	Week 2	(OC)	150	-7.46	0.49	-8.44	-6.49
	Week 3	(OC)	151	-9.74	0.58	-10.89	-8.59
	Week 4	(OC)	154	-10.50	0.62	-11.72	-9.27
	Week 6	(OC)	148	-12.59	0.63	-13.84	-11.33
	Week 8	(OC)	150	-14.55	0.64	-15.81	-13.29
	Last	(LOCF)	159	-13.59	0.67	-14.91	-12.27
ESC	Week 1	(OC)	154	-4.40	0.40	-5.20	-3.61
	Week 2	(OC)	146	-8.20	0.50	-9.18	-7.22
	Week 3	(OC)	143	-10.62	0.60	-11.80	-9.45
	Week 4	(OC)	145	-11.82	0.63	-13.07	-10.58
	Week 6	(OC)	144	-13.74	0.63	-15.00	-12.49
	Week 8	(OC)	145	-15.89	0.64	-17.15	-14.62
	Last	(LOCF)	155	-15.02	0.67	-16.35	-13.69

Table 6.9 Proportion of Patients with  $\geq 50\%$  Reduction in MADRS Total Score for Study 99003

Treatment Group	Visit #		n	MADRS $\geq 50\%$ reduction		95% Confidence Limits	
				n	%	Lower(%)	Upper(%)
PBO	Week 1	(OC)	149	7	4.7	1.9	9.4
	Week 2	(OC)	140	20	14.3	8.9	21.2
	Week 3	(OC)	141	44	31.2	23.7	39.5
	Week 4	(OC)	144	43	29.9	22.5	38.0
	Week 6	(OC)	145	54	37.2	29.4	45.7
	Week 8	(OC)	138	66	47.8	39.3	56.5
	Last	(LOCF)	154	67	43.5	35.5	51.7
GIT	Week 1	(OC)	154	6	3.9	1.4	8.3
	Week 2	(OC)	150	19	12.7	7.8	19.1
	Week 3	(OC)	151	39	25.8	19.1	33.6
	Week 4	(OC)	154	49	31.8	24.6	39.8
	Week 6	(OC)	148	63	42.6	34.5	51.0
	Week 8	(OC)	150	78	52.0	43.7	60.2
	Last	(LOCF)	159	79	49.7	41.7	57.7
ESC	Week 1	(OC)	154	8	5.2	2.3	10.0
	Week 2	(OC)	146	26	17.8	12.0	25.0
	Week 3	(OC)	143	38	26.6	19.5	34.6
	Week 4	(OC)	145	59	40.7	32.6	49.2
	Week 6	(OC)	144	72	50.0	41.6	58.4
	Week 8	(OC)	145	92	63.4	55.1	71.3
	Last	(LOCF)	155	95	61.3	53.1	69.0

Table 6.10 Proportion of Patients with MADRS Total Score ≤ 12 for Study 99003

Treatment Group	Visit #		n	MADRS ≤ 12		95% Confidence Limits	
				n	%	Lower(%)	Upper(%)
PBO	Week 1	(OC)	149	2	1.3	0.2	4.8
	Week 2	(OC)	140	18	12.9	7.8	19.6
	Week 3	(OC)	141	31	22.0	15.5	29.7
	Week 4	(OC)	144	37	25.7	18.8	33.6
	Week 6	(OC)	145	43	29.7	22.4	37.8
	Week 8	(OC)	138	62	44.9	36.5	53.6
	Last	(LOCF)	154	63	40.9	33.1	49.1
CIT	Week 1	(OC)	154	4	2.6	0.7	6.5
	Week 2	(OC)	150	13	8.7	4.7	14.4
	Week 3	(OC)	151	30	19.9	13.8	27.1
	Week 4	(OC)	154	40	26.0	19.2	33.6
	Week 6	(OC)	148	51	34.5	26.8	42.7
	Week 8	(OC)	150	62	41.3	33.4	49.7
	Last	(LOCF)	159	63	39.6	32.0	47.7
ESC	Week 1	(OC)	154	3	1.9	0.4	5.6
	Week 2	(OC)	146	16	11.0	6.4	17.2
	Week 3	(OC)	143	32	22.4	15.8	30.1
	Week 4	(OC)	145	43	29.7	22.4	37.8
	Week 6	(OC)	144	60	41.7	33.5	50.2
	Week 8	(OC)	145	75	51.7	43.3	60.1
	Last	(LOCF)	155	78	50.3	42.2	58.4

Table 6.11 Adjusted Mean Change from Baseline in CGI Severity Scores for Study 99003

Treatment Group	Visit #		n	Least Squares Mean	SE	95% Confidence Limits	
						Lower	Upper
PBO	Week 1	(OC)	149	-0.26	0.06	-0.38	-0.15
	Week 2	(OC)	140	-0.64	0.07	-0.79	-0.49
	Week 3	(OC)	141	-0.86	0.09	-1.03	-0.69
	Week 4	(OC)	144	-0.97	0.09	-1.16	-0.79
	Week 6	(OC)	145	-1.28	0.09	-1.47	-1.10
	Week 8	(OC)	138	-1.54	0.10	-1.73	-1.35
	Last	(LOCF)	154	-1.41	0.09	-1.59	-1.22
CIT	Week 1	(OC)	153	-0.33	0.06	-0.44	-0.22
	Week 2	(OC)	151	-0.67	0.07	-0.82	-0.53
	Week 3	(OC)	151	-1.03	0.08	-1.19	-0.86
	Week 4	(OC)	154	-1.14	0.09	-1.32	-0.97
	Week 6	(OC)	148	-1.40	0.09	-1.59	-1.22
	Week 8	(OC)	150	-1.68	0.09	-1.86	-1.49
	Last	(LOCF)	159	-1.56	0.09	-1.74	-1.37
ESC	Week 1	(OC)	154	-0.43	0.06	-0.54	-0.32
	Week 2	(OC)	146	-0.86	0.07	-1.00	-0.71
	Week 3	(OC)	143	-1.20	0.09	-1.37	-1.03
	Week 4	(OC)	145	-1.28	0.09	-1.46	-1.10
	Week 6	(OC)	144	-1.52	0.09	-1.70	-1.33
	Week 8	(OC)	145	-1.89	0.09	-2.07	-1.71
	Last	(LOCF)	155	-1.79	0.09	-1.98	-1.61

Table 6.12 Proportion of Patients with CGI Severity Scores of 1 or 2 for Study 99003

Treatment Group	Visit #		n	CGI-S 1 or 2*		95% Confidence Limits	
				n	%	Lower(%)	Upper(%)
PBO	Week 1	(OC)	149	7	4.7	1.9	9.4
	Week 2	(OC)	140	19	13.6	8.4	20.4
	Week 3	(OC)	141	30	21.3	14.8	29.0
	Week 4	(OC)	144	36	25.0	18.2	32.9
	Week 6	(OC)	145	52	35.9	28.1	44.2
	Week 8	(OC)	138	62	44.9	36.5	53.6
	Last	(LOCF)	154	64	41.6	33.7	49.8
CIT	Week 1	(OC)	153	4	2.6	0.7	6.6
	Week 2	(OC)	151	16	10.6	6.2	16.6
	Week 3	(OC)	151	35	23.2	16.7	30.7
	Week 4	(OC)	154	45	29.2	22.2	37.1
	Week 6	(OC)	148	54	36.5	28.7	44.8
	Week 8	(OC)	150	74	49.3	41.1	57.6
	Last	(LOCF)	159	75	47.2	39.2	55.2
ESC	Week 1	(OC)	154	7	4.5	1.8	9.1
	Week 2	(OC)	146	24	16.4	10.8	23.5
	Week 3	(OC)	143	42	29.4	22.1	37.6
	Week 4	(OC)	145	48	33.1	25.5	41.4
	Week 6	(OC)	144	59	41.0	32.9	49.5
	Week 8	(OC)	145	80	55.2	46.7	63.4
	Last	(LOCF)	155	82	52.9	44.7	61.0

Table 6.13 Adjusted Mean CGI Improvement Scores for Study 99003

Treatment Group	Visit #		n	Least Squares Mean	SE	95% Confidence Limits	
						Lower	Upper
PBO	Week 1	(OC)	149	3.49	0.08	3.33	3.65
	Week 2	(OC)	140	3.07	0.09	2.90	3.25
	Week 3	(OC)	141	2.89	0.09	2.70	3.07
	Week 4	(OC)	144	2.89	0.10	2.70	3.08
	Week 6	(OC)	145	2.58	0.09	2.41	2.75
	Week 8	(OC)	138	2.32	0.09	2.15	2.49
	Last	(LOCF)	154	2.51	0.09	2.33	2.68
CIT	Week 1	(OC)	153	3.36	0.08	3.20	3.52
	Week 2	(OC)	151	3.03	0.08	2.86	3.20
	Week 3	(OC)	151	2.74	0.09	2.57	2.92
	Week 4	(OC)	154	2.67	0.09	2.48	2.86
	Week 6	(OC)	148	2.38	0.09	2.21	2.56
	Week 8	(OC)	150	2.05	0.08	1.89	2.22
	Last	(LOCF)	159	2.20	0.09	2.02	2.38
ESC	Week 1	(OC)	154	3.26	0.08	3.10	3.41
	Week 2	(OC)	146	2.80	0.09	2.63	2.97
	Week 3	(OC)	143	2.55	0.09	2.37	2.73
	Week 4	(OC)	145	2.45	0.10	2.26	2.64
	Week 6	(OC)	144	2.29	0.09	2.11	2.46
	Week 8	(OC)	145	1.97	0.09	1.80	2.13
	Last	(LOCF)	155	2.08	0.09	1.90	2.26

Table 6.14 Proportion of Patients with CGI Improvement Scores of 1 or 2 for Study 99003

Treatment Group	Visit #	n	CGI-I 1 or 2*		95% Confidence Limits		
			n	%	Lower	Upper	
PBO	Week 1	(OC)	149	20	13.4	8.4	20.0
	Week 2	(OC)	140	44	31.4	23.9	39.8
	Week 3	(OC)	141	54	38.3	30.2	46.9
	Week 4	(OC)	144	57	39.6	31.5	48.1
	Week 6	(OC)	145	73	50.3	41.9	58.7
	Week 8	(OC)	138	83	60.1	51.5	68.4
	Last	(LOCF)	154	84	54.5	46.3	62.6
CIT	Week 1	(OC)	153	28	18.3	12.5	25.4
	Week 2	(OC)	151	41	27.2	20.2	35.0
	Week 3	(OC)	151	71	47.0	38.9	55.3
	Week 4	(OC)	154	74	48.1	39.9	56.2
	Week 6	(OC)	148	90	60.8	52.5	68.7
	Week 8	(OC)	150	102	68.0	59.9	75.4
	Last	(LOCF)	159	103	64.8	56.8	72.2
ESC	Week 1	(OC)	154	31	20.1	14.1	27.3
	Week 2	(OC)	146	62	42.5	34.3	50.9
	Week 3	(OC)	143	75	52.4	43.9	60.9
	Week 4	(OC)	145	82	56.6	48.1	64.8
	Week 6	(OC)	144	91	63.2	54.8	71.1
	Week 8	(OC)	145	110	75.9	68.1	82.6
	Last	(LOCF)	155	113	72.9	65.2	79.7

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-323/S-007 & 21-365/S-001**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

EXCLUSIVITY SUMMARY for NDA # 21-323/SE8-007 & 21-365/SE8-001

Trade Name Lexapro Tablets (NDA 21-323) and Solution (NDA 21-365)

Generic Name escitalopram oxalate

Applicant Name Forest Pharmaceuticals

HFD-120

Approval Date 12-18-03

**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 / X/

b) Is it an effectiveness supplement? YES /\_X\_/ NO /\_X\_/

If yes, what type(SE1, SE2, etc.)? SE8

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 /  /

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 /  /

**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 /  /

If yes, NDA # 21-323 Drug Name Lexapro

Lexapro was approved for the indication of major depressive disorder on 8-14-02. The approval was based, in part, on the Agency's approval of Celexa (citalopram HBr) which is the racemate of escitalopram. These efficacy supplements provided for the efficacy study reports from Studies 99001 & 99003 as additional trials supporting the efficacy of escitalopram in the treatment of major depressive disorder.

**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 /  /

**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 /\_\_/ NO /\_\_/

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

NDA # \_\_\_\_\_

NDA #

NDA #

2. Combination product.

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 / \_\_\_ /

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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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

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 /\_\_\_/ 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 /\_\_\_/                      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 /\_\_\_/                      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 /\_\_\_/

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 /\_\_\_/

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 #

Investigation #2, Study #

Investigation #3, Study #

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 /\_\_\_/

Investigation #2      YES /\_\_\_/      NO /\_\_\_/

Investigation #3      YES /\_\_\_/      NO /\_\_\_/

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 /\_\_\_/  
Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/  
Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

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 # 1, Study #  
Investigation # \_\_, Study #  
Investigation # \_\_, Study #

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 /\_\_\_/ ! NO /\_\_\_/ Explain:

Investigation #2  
IND # \_\_\_\_\_ YES /\_\_\_/ ! 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: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Title:

Date

Signature of Office of Division Director

Date

cc:  
Archival NDAs 21-323/S-007 & 21-365/S-001

HFD-120/Division File  
HFD-120/David  
HFD-093/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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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.

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

Page 2

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/

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Russell Katz

4/8/04 12:04:26 PM

**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/

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Paul David  
3/30/04 10:16:18 AM  
CSO

Robbin Nighswander  
3/30/04 12:52:54 PM  
CSO

**David, Paul A**

---

**From:** Andrew.Friedman@frx.com  
**Sent:** Tuesday, December 16, 2003 3:21 PM  
**To:** DAVID@cder.fda.gov  
**Subject:** Lexapro Package Insert - GAD & Efficacy 12-16-03

Dear Paul,

I am happy to tell you that Forest agrees to make the changes to the Lexapro package insert we discussed this morning. Attached please find all of the revisions outlined in a one document (Highlighted and Strikethrough marks represent the current changes in question).

<<lexapro changes 12-16-03.doc>>

If you have any questions please do not hesitate to contact me. I will be checking voice mail throughout the day or can be reached at [ ] [ ]

*Andrew F. Friedman, PharmD*  
*Manager, Regulatory Affairs*  
*Forest Research Institute*  
*Tel: (201) 386-2117*

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## **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 ~~depression~~ **depressive disorder**. The primary outcome in all three studies was change from baseline to endpoint in the Montgomery Asberg Depression Rating Scale (MADRS).

### **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 (~~HAMA~~) (~~HAM-A~~).

### **Activation of Mania/Hypomania**

In placebo-controlled trials of LEXAPRO in ~~MDD~~ **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.

### **Information for Patients (6<sup>th</sup> paragraph down in this section)**

Patients should be cautioned about the concomitant use of LEXAPRO and ~~nonsteroidal anti-inflammatory drugs or aspirin, NSAIDs, aspirin,~~ **nonsteroidal anti-inflammatory drugs or aspirin, 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.

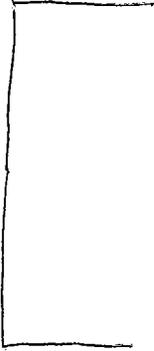
### **Impairment of Fertility (FDA feels this wording is clearer)**

When racemic citalopram was administered orally to ~~male and female rats 16/24~~ **(males/females), 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  $\geq 32$  mg/kg/day. Gestation duration was increased at 48 mg/kg/day.

~~Delete the following and keep original wording pertaining to citalopram – submit supplement in near future to add postmarketing events with escitalopram~~

**Events Reported Subsequent to the Marketing of Escitalopram**



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/s/

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Paul David  
12/22/03 01:07:09 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**

December 11, 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

**NDA: 21-323/ S-007 Lexapro™ (Escitalopram Oxalate) Tablets**  
**NDA: 21-365/S-001 Lexapro™ (Escitalopram Oxalate) Oral Solution**  
**Re: Amendment to Pending Application: Efficacy Supplement**

Dear Dr. Katz:

Reference is made to supplemental NDA 21-323/S-007 & 21-365/S-001 submitted on February 6, 2003 and to an FDA/Forest teleconference held on December 11, 2003. During the teleconference the Lexapro package insert was discussed and wording agreed upon which affects pending supplemental applications (Supplemental MDD Efficacy trial data and Generalized Anxiety Disorder indication).

With this letter, please find Forest's revised draft package insert incorporating the agreed upon language (**Attachment 1**). In addition, please find one diskette that contains an electronic copy of this cover letter, Form FDA 356h, and the draft labeling. The diskette has been scanned and is free from computer viruses.

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, PharmD  
Manager, Regulatory Affairs  
[Andrew.Friedman@frx.com](mailto:Andrew.Friedman@frx.com)

Desk Copies w/ Attachments: Paul David, RPh., Senior Regulatory Project Manager, HFD-120  
Richardae Taylor, PharmD, Regulatory Project Manager, HFD-120



**FOREST LABORATORIES, INC.**  
Harborside Financial Center  
Plaza Three, Suite 602  
Jersey City, New Jersey 07311

**Direct Line: (201) 386-2117**  
**Fax: (201) 524-9711**

December 4, 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

**NDA: 21-323/ S-007 Lexapro™ (Escitalopram Oxalate) Tablets**  
**NDA: 21-365/S-001 Lexapro™ (Escitalopram Oxalate) Oral Solution**  
**Re: Amendment to Pending Application: Efficacy Supplement**  
**Re: REQUEST FOR TELECONFERENCE**

Dear Dr. Katz:

Reference is made to sNDA's 21-323/S-007 & 21-365/S-001 and to the approvable letter dated November 25, 2003.

With this letter Forest Laboratories submits draft labeling incorporating all the Division's suggested additions with minor Forest modifications (highlighted), including the "class labeling statements". These modifications to the package insert affect pending supplemental applications (Supplemental MDD Efficacy trial data and Generalized Anxiety Disorder indication) that Forest would like resolved as soon as possible.

In order to resolve the class labeling expeditiously, Forest requests a teleconference with the Division during the week of December 8<sup>th</sup>, 2003 to discuss and agree upon the attached proposed labeling (**Attachment 1**). Enclosed please find one diskette that contains the draft labeling and appropriate forms. The diskette has been scanned and is free from computer viruses.

Forest will follow up with FDA's Mr. Paul David to arrange a mutually agreeable time for the teleconference.

If there are any questions related to this submission, please contact me at (201) 386-2117 or in my absence Michael Macalush at (201) 386-2007.

Sincerely,

Andrew F. Friedman, PharmD  
Manager, Regulatory Affairs

Desk Copy w/Attachment: Mr. Paul David, RPh., Senior Regulatory Health Project Manager, HFD-120

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: November 12, 2003

TO: Paul David, R.Ph., Senior Regulatory Health Project Manager  
Cara Alfaro, Pharm.D., Clinical Reviewer  
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/SE8-007  
NDA 21-365/SE8-001

APPLICANT: Forest Laboratories, Inc.

DRUG: Escitalopram oxalate (Lexapro) Tablets and Oral Solution

THERAPEUTIC CLASSIFICATION: Type S

INDICATION: Major Depressive Disorder (MDD)

CONSULTATION REQUEST DATE: April 8, 2003

ACTION GOAL DATE: December 7, 2003

**I. BACKGROUND:**

Escitalopram oxalate (Lexapro<sup>TM</sup>) is the S-entiomer of the selective serotonin reuptake inhibitor citalopram. The efficacy of Lexapro in the treatment of major depressive disorder was established, in part, on the basis of extrapolation from the established effectiveness of racemic citalopram. The efficacy of escitalopram was shown in an 8-week controlled trial of outpatients whose diagnoses corresponded most closely to the DSM-IV category of major depressive disorder. In this supplemental application, the sponsor has included the results of protocol 99001 ("A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg escitalopram in outpatients with major depressive disorder") and 99003 ("A double-blind,



**2. Site #2002 (Dr. Sild, Tallin, Estonia): Data Acceptable**

- a. What was inspected: At this site, 19 subjects enrolled in the study.
- b. Limitations of inspection: the source documents were written in Estonian.
- c. General observations/commentary: No Form FDA 483 was issued. All subjects signed the informed consent. 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. No underreporting of adverse events was noted. Except for minor instances at Dr. Wade's site as stated above, data from these centers that had been inspected appear acceptable for use in support of this supplemental NDA.

[Note: Should the EIR and exhibits from the audits, 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 completed; EIR still pending

---

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/SE8-007; NDA 21-365/SE8-001

HFD-45/Division File/Reading File  
HFD-45/Program Management Staff (electronic copy)  
HFD-46/U  
HFD-46/Khin  
HFD-46/George GCPB1 Files

rd:NK:11/12/03

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/s/

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Ni Aye Khin  
11/12/03 02:08:42 PM  
MEDICAL OFFICER

Khin U  
11/12/03 02:13:37 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

Alan Wade, M.D.  
Riverside Medi Park  
Beardmore Street  
Clydebank  
Glasgow G81, Scotland

DEC - 8 2003

Dear Dr. Wade:

Between October 20 and 23, 2003, Ms. Barbara Frazier and Dr. Ni A. Khin, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol 99001 entitled "A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg escitalopram in outpatients with major depressive 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.

We understand you did not perform this study under a U.S. Investigational New Drug Application (IND). For your future reference, however, we are providing comments so that you will be aware of FDA's requirements for clinical studies conducted under a U.S. IND.

We provide these comments based on our review of the establishment inspection report and the documents submitted with that report. The provisions of the U.S. Code of Federal Regulations (CFR) that would have been violated had the study been conducted under an IND are provided below for future reference.

1. You did not adhere to the investigational plan [21 CFR 312.60].
  - a) You did not obtain pregnancy test for two subjects (156 and 308) prior to randomization.
  - b) You enrolled subject 308 who had a low thyroid stimulating hormone level of 0.1 (normal range 0.4 to 5.5).

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- Alan Wade, M.D.

We appreciate the cooperation shown our FDA personnel 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,

A handwritten signature in cursive script, appearing to read "Khin Maung U, M.D.", with a horizontal line underneath.

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- Alan Wade, M.D.

FEI: 3004044889

Field Classification: Refer to Center

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

Deficiencies noted:

failure to adhere to protocol (05)

cc:

HFA-224

HFD-120 Doc.Rm. NDA#21-323/SE8-007

HFD-120 Review Div.Dir. Katz

HFD-120 Reveiwer Alfaro

HFD-120 PM David

HFD-46 c/r/s/ GCP File #11049

HFD-46 MO Khin

HFR-SE150 DIB Todd-Murrell

HFR-SE150 BIMO Hubbard

HFR-SE1535 Field Investigator Frazier

HFC-130 Kadar

GCF-1 Seth Ray

r/d: NK 11/24/03

reviewed: KMU 11/24/03

f/t: SG 11/28/03

O:\NK\\_Letters\Wade.vai.doc

Reviewer Note to Rev. Div. M.O.

- Dr. Wade is the principal investigator of the study and the Director of Clinical Pharmacology Services (CPS).
- 
- A total of 82 subjects were screened and 72 subjects were randomized in the study.
- An audit of 42 subjects' records including 38 randomized subjects and 4 screen failures was conducted.
- No Form FDA 483 was issued at the end of inspection.
- However, the discussion at closeout of inspection included: 1) Two of the female subjects enrolled in the study were randomized without any pregnancy test having been done (156 and 308); 2) The screening laboratory results of subject 003 showed low thyroid stimulating hormone level of 0.1 (normal range 0.4 to 5.5), yet the subject was enrolled in the study. No repeat TSH level or thyroid function tests were done. Instead, Dr. Wade reviewed the screening labs, signed off as no clinical significance and enrolled the subject.
- Overall, data appear acceptable.

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/s/

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Khin U  
12/10/03 10:58:36 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Andres Sild, M.D.  
North Estonian Regional Hospital Psychiatry Clinic  
Paldiski mt. 52  
Tallin, Estonia

Food and Drug Administration  
Rockville MD 20857

DEC - 8 2003

Dear Dr. Sild:

Between October 13 and 15, 2003, Ms. Barbara Frazier, representing the United States Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol 99001 entitled "A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of 10 mg escitalopram in outpatients with major depressive 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.

We understand you did not perform this study under a U.S. Investigational New Drug Application (IND). For your future reference, however, we are providing comments so that you will be aware of FDA's requirements for clinical studies conducted under a U.S. IND.

We provide these comments based on our review of the establishment inspection report and the documents submitted with that report. The provisions of the U.S. Code of Federal Regulations (CFR) that would have been violated had the study been conducted under an IND are provided below for future reference.

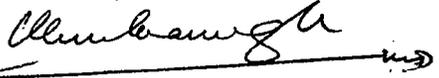
1. You did not maintain adequate and accurate records [21 CFR 312.62(b)].
  - a) You did not maintain the faxed laboratory reports reviewed by your subinvestigator, Dr.   for eight subjects prior to their randomization visit, as source documents.
  - b) There were minor discrepancies between the source documents and the case report forms for the Clinical Global Impression scores recorded for 2 subjects: #314(visit 7) and #415(visit 2).

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- Andres Sild, M.D.

We appreciate the cooperation shown Investigator Frazier 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,

A handwritten signature in cursive script, appearing to read "Khin Maung U", with a horizontal line underneath it.

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

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/s/

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Khin U  
12/8/03 11:38:26 AM



**FOREST LABORATORIES, INC.**  
Harborside Financial Center  
Plaza Three, Suite 602  
Jersey City, New Jersey 07311

Direct Line: (201) 386-2117  
Fax: (201) 524-9711

September 18, 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

**NDA: 21-323/ S-007 Lexapro™ (Escitalopram Oxalate) Tablets**  
**NDA: 21-365/S-001 Lexapro™ (Escitalopram Oxalate) Oral Solution**  
**Re: Response to FDA Request for Information: Statistical Request for Efficacy Supplement**  
**(Request received via e-mail 7-31-03)**

Dear Dr. Katz:

Reference is made to supplemental NDA 21-323/S-007 & 21-365/S-001 submitted on February 6, 2003 and to FDA's Request for Information received via e-mail on July 31, 2003 regarding SAS algorithm and SAS code on LOCF analysis for the above mentioned Lexapro Efficacy Supplements.

With this letter, please find Forest's complete response to the requested information (**Appendix 1**). In addition, please find one compact disc (CD) that contains the requested SAS program files for the LOCF analyses together with the output files.

The content on the CD provided with this submission has been protected and is free from computer viruses using McAfee Virus Scan Anti-Virus software.

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](mailto:Andrew.Friedman@frx.com)

Desk Copies w/ Att: Mr. Paul David, RPh., Senior Regulatory Project Manager, HFD-120

## DSI CONSULT: Request for Clinical Inspections

**Date:** April 8, 2003

**To:** Ni Khin, MD, GCPB Reviewer/HFD-47

**Through:** Martin H. Cohen, M.D., Acting Director, DSI, HFD-45  
Russell Katz, M.D., Director, HFD-120

**From:** Paul David, Senior Regulatory Health Project Manager, HFD-120

**Subject:** **Request for Clinical Inspections**  
NDA 21-323/SE8-007  
NDA 21-365/SE8-001  
Forest Laboratories, Inc.  
Lexapro (escitalopram oxalate) Tablets and Solution

### **Protocol/Site Identification:**

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are attached to this consult.

These supplements provide for the efficacy study reports from Studies 99001 & 99003 as additional trials supporting the efficacy of escitalopram in the treatment of major depressive disorder.

### **International Inspections:**

We have requested inspections because (please check appropriate statements):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: SPECIFY

NDA 21-323/SE8-007 & 21-365/SE8-001

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Request for Clinical Inspections

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **October 2003**. We intend to issue an action letter on these applications by (action goal date) **December 7, 2003**.

Should you require any additional information, please contact Paul David at 594-5530.

Ongoing Clinical Trials		
Center No.	Investigator	Center Address
NON-U.S. STUDIES		
STUDY 99001		
1001	Dr Stanley Kutcher Dr [ ]	Charleswood Medical Clinic 3360 Roblin BLVD Winipeg, Manitoba R3R 0C5 Canada
1010	Dr Stanley Kutcher Dr [ ] Dr [ ]	Polyclinic Professional Centre 199 Grafton Street Charlottetown Prince Edward Island C1A 1L2 Canada
1010	Dr Stanley Kutcher Dr [ ] Dr [ ]	Cornwall Medical Centre PO Box 100 Cornwall Prince Edward Island COA 1H0 Canada
1020	Dr Stanley Kutcher Dr [ ]	Riverview Medical Clinic 720 Coverdale Road Riverview, Moun-ton New Brunswick E1B 3L4 Canada
1020	Dr Stanley Kutcher Dr [ ]	Mountain Road Suite 102 Moun-ton, New Brunswick E1C-2R4 Canada
1020	Dr Stanley Kutcher Dr [ ]	040 St-Georges Street Moun-ton, New Brunswick E1C 1X6 Canada
1201	Dr. Alan Wade	CPS Ltd Riverside Medi Park Beardmore Street Clydebank Glasgow G81 Scotland

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/s/

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Russell Katz  
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NDA 21-323/S-007  
NDA 21-365/S-001

**PRIOR APPROVAL SUPPLEMENT**

Forest Laboratories, Inc.  
Attention: Tracey Varner  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza Three, Suite 602  
Jersey City, NJ 07311

Dear Ms. Varner:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lexapro (escitalopram oxalate) Tablets (NDA 21-323) and Lexapro (escitalopram oxalate) Oral Solution (NDA 21-365)

Date of Supplement: February 6, 2003

Date of Receipt: February 7, 2003

These supplements provide for the efficacy study reports from Studies 99001 & 99003 as additional trials supporting the efficacy of escitalopram in the treatment of major depressive disorder.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 8, 2003 in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be December 7, 2003.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
1451 Rockville Pike  
Rockville, Maryland 20852-1420

If you have any questions, call me at (301) 594-5530.

Sincerely,

*{See appended electronic signature page}*

Paul David, R.Ph.  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Paul David  
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