CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

Trade Name: Lexapro

Generic Name: Escitalopram Oxalate

Sponsor: FOREST LABORATORIES INC

Approval Date: 3/19/2009

Indications: Acute and Maintenance Treatment of Major Depressive Disorder (MDD) in adults and adolescents aged 12-17 years

Acute Treatment of Generalized Anxiety Disorder (GAD) in adults (1.2)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-323/S-030/S-031
NDA 21-365/S-021/S-022

Forest Laboratories, Inc.
Attention: Maricarmen Raposo
Senior Associate, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Ms. Raposo:

Please refer to your supplemental new drug applications dated May 22, 2008, received May 23, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) 5 mg, 10 mg, and 20 mg tablets (NDA 21-323) and Lexapro (escitalopram oxalate) 5 mg/ml Oral solution (NDA 21-365).

We acknowledge receipt of your submissions dated August 13, 2008, September 19, 2008, September 26, 2008, October 2, 2008, December 4, 2008, December 11, 2008, December 19, 2008, December 24, 2008, January 15, 2009, February 6, 2009, February 9, 2009, February 23, 3009, and March 6, 2009.

These supplemental new drug applications provide for the use of Lexapro (escitalopram oxalate) tablets and solution for the acute and maintenance treatment of adolescent major depressive disorder (MDD).

We have completed our review of your submissions as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling, unless we notify you otherwise.

CONTENT OF LABELING: STRUCTURED PRODUCT LABELING [SPL]

The final printed labeling (FPL) must be identical to the enclosed labeling [package insert and Medication Guide], and must be formatted in accordance with the requirements of 21 CFR 201.66.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured Product Labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html , that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved NDA labeling under NDAs 21-323/S-030/S-031 & 21-365/S-021/S-022".

POSTMARKETING COMMITMENT

We remind you of your following postmarketing commitment agreed upon in your submission dated February 23, 2009. This commitment is listed below.

1. Long-Term Safety Study

   An open-label, 24-week safety study with escitalopram in children ages 7-11 .

   PROTOCOL SUBMISSION: 14 months from the date of this letter
   STUDY INITIATION: 18 months from the date of this letter
   FINAL REPORT SUBMISSION: 5 years from the date of this letter.

Reference is also made to a teleconference between Forest and the Agency on March 10, 2009, regarding our suggestion that Forest conduct, as a Phase 4 Postmarketing Commitment, a 6 week double blind randomized safety and efficacy study in children ages 7-11 with Lexapro. This would be in addition to your proposed open label longer-term safety study in children. While we acknowledge your reluctance to conduct the 6 week efficacy study, we hope you will reconsider, since we feel this would be a benefit to the public health. As you know, Lexapro is already being used to treat MDD in children, and such use is likely to increase with the approval of a claim for MDD in adolescents.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

LETTERS TO HEALTH CARE PROFESSIONALS

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

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

INTRODUCTORY PROMOTIONAL MATERIALS

In addition, submit three copies of the introductory promotional materials that you propose to use for this indication. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

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 LCDR Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Product Labeling & Medication Guide

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

/s/

Thomas Laughren
3/19/2009 03:59:57 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Lexapro® safely and effectively. See full prescribing information for Lexapro®

Lexapro® (escitalopram oxalate) Tablets
Lexapro® (escitalopram oxalate) Oral Solution
Initial U.S. Approval: 2002

WARNING: Suicidality and Antidepressant Drugs
See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Lexapro is not approved for use in pediatric patients less than 12 years of age (5.1).

----------RECENT MAJOR CHANGES----------

Indication and Usage, Major Depressive Disorder (1.1)	03/2009
Dosage and Administration, Major Depressive Disorder (2.1)	03/2009
Warnings and Precautions, Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions (5.2)	01/2009
Warnings and Precaution, Hyponatremia (5.6)	03/2008
Warnings and Precautions, Abnormal Bleeding (5.7)	03/2008

----------INDICATIONS AND USAGE----------
Lexapro® is a selective serotonin reuptake inhibitor (SSRI) indicated for:
- Acute and Maintenance Treatment of Major Depressive Disorder (MDD) in adults and adolescents aged 12-17 years (1.1)
- Acute Treatment of Generalized Anxiety Disorder (GAD) in adults (1.2)

----------DOSAGE AND ADMINISTRATION----------
Lexapro should generally be administered once daily, morning or evening with or without food (2.1, 2.2).

Indication	Recommended Dose
MDD (2.1)	
Adolescents (2.1)	Initial: 10 mg once daily Recommended: 10 mg once daily Maximum: 20 mg once daily
Adults (2.1)	Initial: 10 mg once daily Recommended: 10 mg once daily Maximum: 20 mg once daily
GAD (2.2)	
Adults (2.2)	Initial: 10 mg once daily Recommended: 10 mg once daily

- No additional benefits seen at 20 mg/day dose (2.1).
- 10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment (2.3).
- No dosage adjustment for patients with mild or moderate renal impairment. Use caution in patients with severe renal impairment (2.3).
- Discontinuing Lexapro: A gradual dose reduction is recommended (2.4).

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 5 mg, 10 mg (scored) and 20 mg (scored) (3.1)
- Oral solution: 1 mg per mL (3.2)

----------CONTRAINDICATIONS----------
- Monoamine Oxidase Inhibitors: Do not use with an MAOI or within 14 days of stopping an MAOI. Allow 14 days after stopping Lexapro before starting an MAOI (4.1, 5.10).
- Pimozide: Do not use concomitantly (4.2, 7.10).
- Known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients (4.3).

----------WARNINGS AND PRECAUTIONS----------
- Clinical Worsening/Suicide Risk: Monitor for clinical worsening, suicidality and unusual change in behavior, especially, during the initial few months of therapy or at times of dose changes (5.1).
- Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: Manage with immediate discontinuation and continuing monitoring (5.2).
- Discontinuation of Treatment with Lexapro: A gradual reduction in dose rather than abrupt cessation is recommended whenever possible (5.3).
- Seizures: Prescribe with care in patients with a history of seizure (5.4).
- Activation of Mania/Hypomania: Use cautiously in patients with a history of mania (5.5).
- Hyponatremia: Can occur in association with SIADH (5.6).
- Abnormal Bleeding: Use caution in concomitant use with NSAIDs, aspirin, warfarin or other drugs that affect coagulation (5.7).
- Interference with Cognitive and Motor Performance: Use caution when operating machinery (5.8).
- Use in Patients with Concomitant Illness: Use caution in patients with diseases or conditions that produce altered metabolism or hemodynamic responses (5.9).

----------ADVERSE REACTIONS----------
Most commonly observed adverse reactions (incidence ≥ 5% and at least twice the incidence of placebo patients) are : insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue and somnolence, decreased libido, and anorgasmia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Forest Laboratories Inc. at 1-800-678-1605, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
Concomitant use with SSRIs, SNRIs or Tryptophan is not recommended (7.1).
Use caution when concomitant use with drugs that affect Hemostasis (NSAIDs, Aspiring, Warfarin) (7.6).

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus (8.1).
Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3)
Pediatric Use: Safety and effectiveness of Lexapro has not been established in pediatric MDD patients less than 12 years of age (8.4).

See 17 for PATIENT COUNSELING INFORMATION andMedication Guide.

Revised: 03/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age. ***[See Warnings and Precautions: Clinical Worsening and Suicide Risk (5.1), Patient Counseling Information: Information for Patients (17.1), and Used in Specific Populations: Pediatric Use (8.4)].***

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

Lexapro (escitalopram) is indicated for the acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age [*see Clinical Studies (14.1)*].

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.

1.2 Generalized Anxiety Disorder

Lexapro is indicated for the acute treatment of Generalized Anxiety Disorder (GAD) in adults [*see Clinical Studies (14.2)*].

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.

2 DOSAGE AND ADMINISTRATION

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

2.1 Major Depressive Disorder

Initial Treatment

Adolescents

The recommended dose of Lexapro is 10 mg once daily. A flexible-dose trial of Lexapro (10 to 20 mg/day) demonstrated the effectiveness of Lexapro [*see Clinical Studies (14.1)*]. If the dose is increased to 20 mg, this should occur after a minimum of three weeks.

Adults

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 Studies (14.1)*]. If the dose is increased to 20 mg, this should occur after a minimum of one week.

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 in adults 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 Studies (14.1*)]. 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. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.2 Generalized Anxiety Disorder

Initial Treatment

Adults

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.

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 re-evaluate the long-term usefulness of the drug for the individual patient.

2.3 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.

2.4 Discontinuation of Treatment with Lexapro

Symptoms associated with discontinuation of Lexapro and other SSRIs and SNRIs have been reported [*see Warnings and Precautions (5.3)*]. 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.

2.5 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 an MAOI [*see Contraindications (4.1) and Warnings and Precautions (5.10)*].

3 DOSAGE FORMS AND STRENGTHS

3.1 Tablets

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. Imprinted with "FL" on one side and either "5", “10”, or “20” on the other side according to their respective strengths.

3.2 Oral Solution

Lexapro oral solution contains escitalopram oxalate equivalent to 1 mg/mL escitalopram base.

4 CONTRAINDICATIONS

4.1 Monoamine oxidase inhibitors (MAOIs)

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated [*see Warnings and Precautions (5.10)*].

4.2 Pimozide

Concomitant use in patients taking pimozide is contraindicated [*see Drug Interactions (7.10)*].

4.3 Hypersensitivity to escitalopram or citalopram

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

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1**.

TABLE 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Dosage and Administration (2.4)*].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers [*see also Patient Counseling Information (17.1)*]. 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.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Lexapro is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Lexapro treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated. If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended. Treatment with Lexapro and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 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 (2.4)*].

5.4 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.

5.5 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.

5.6 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Lexapro. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Lexapro was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Geriatric Use (8.5)*]. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

5.7 Abnormal Bleeding

SSRIs and SNRIs, including Lexapro, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of

gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation.

5.8 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.

5.9 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 (2.3)*].

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 (2.3)*].

5.10 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 an 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 an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI.

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Clinical Trial Data Sources

Pediatrics (6 -17 years)

Adverse events were collected in 576 pediatric patients (286 Lexapro, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Lexapro in pediatric patients less than 12 years of age has not been established.

Adults
Adverse events 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 reactions 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
Pediatrics (6 -17 years)
Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Lexapro and 1% of 290 patients receiving placebo. The most common adverse event (incidence at least 1% for Lexapro and greater than placebo) associated with discontinuation was insomnia (1% Lexapro, 0% placebo).

Adults
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 that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients).

Generalized Anxiety Disorder
Adults
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 Reactions in Placebo-Controlled Clinical Trials

Major Depressive Disorder
Pediatrics (6 -17 years)
The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse reactions (excluding those which appear in Table 2 and those for which the coded terms were uninformative or misleading) were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.

Adults

The most commonly observed adverse reactions 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.

Table 2 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.

TABLE 2

Treatment-Emergent Adverse Reactions observed with a frequency of ≥ 2% and greater than placebo for Major Depressive Disorder

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

[1]Primarily ejaculatory delay.

[2]Denominator used was for males only (N=225 Lexapro; N=188 placebo).

[3]Denominator used was for females only (N=490 Lexapro; N=404 placebo).

Generalized Anxiety Disorder

Adults

The most commonly observed adverse reactions 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.

Table 3 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.

TABLE 3		
Treatment-Emergent Adverse Reactions observed with a frequency of ≥ 2% and greater than placebo for Generalized Anxiety Disorder		
Adverse Reactions	**Lexapro (N=429) %**	**Placebo (N=427) %**
Autonomic Nervous System Disorders		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal System Disorder		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Respiratory System Disorders		
Yawning	2%	1%
Urogenital		
Ejaculation Disorder[1,2]	14%	2%
Anorgasmia[3]	6%	<1%
Menstrual Disorder	2%	1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=182 Lexapro; N=195 placebo).

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

Dose Dependency of Adverse Reactions

The potential dose dependency of common adverse reactions (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse reactions 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 4 shows common adverse reactions that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group.

TABLE 4

Incidence of Common Adverse Reactions in Patients with Major Depressive Disorder

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

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

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

TABLE 5

Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials

Adverse Event	Lexapro	Placebo
	In Males Only	
	(N=407)	(N=383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	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 Reactions Observed During the Premarketing Evaluation of Lexapro

Following is a list of 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. The listing does not include those events already listed in **Tables 2 & 3**, those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Events are categorized by body system. Events of major clinical importance are described in the Warnings and Precautions section (5).

Cardiovascular - hypertension, palpitation.

Central and Peripheral Nervous System Disorders - light-headed feeling, migraine.

Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis.

General - allergy, chest pain, fever, hot flushes, pain in limb.

Metabolic and Nutritional Disorders - increased weight.,

Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness..

Psychiatric Disorders - appetite increased, , concentration impaired, irritability.

Reproductive Disorders/Female - menstrual cramps, menstrual disorder.

Respiratory System Disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache.

Skin and Appendages Disorders - rash.

Special Senses - vision blurred, tinnitus.

Urinary System Disorders - urinary frequency, urinary tract infection.

6.2 Post-Marketing Experience

Adverse Reactions Reported Subsequent to the Marketing of Escitalopram

The following additional adverse reactions have been identified from spontaneous reports of escitalopram received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include:

Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia.

Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia.

Ear and labyrinth disorders: vertigo

Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH.

Eye Disorders: diplopia, glaucoma, mydriasis, visual disturbance.

Gastrointestinal Disorder: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage.

General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise.

Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis.

Immune System Disorders: allergic reaction, anaphylaxis.

Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased.

Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia.

Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis.

Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor.

Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion.

Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency.

Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention.

Reproductive System and Breast Disorders: menorrhagia, priapism.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn.

Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria.

Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

7 DRUG INTERACTIONS

7.1 Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort [*see Warnings and Precautions (5.2)*]. The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended.

7.2 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions (5.2)*].

7.3 CNS Drugs

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

7.4 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.

7.5 Monoamine Oxidase Inhibitors (MAOIs)

[*see Contraindications (4.1) and Warnings and Precautions (5.10)*].

7.6 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 may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Lexapro is initiated or discontinued.

7.7 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.

7.8 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.

7.9 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.

7.10 Pimozide and Celexa

In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

7.11 Sumatriptan

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

7.12 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.

7.13 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.

7.14 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.

7.15 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.

7.16 Ketoconazole

Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

7.17 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.

7.18 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.

7.19 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_{max} 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.

7.20 Metoprolol

Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} 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.

7.21 Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and escitalopram.

8 USE IN SPECIFIC POPULATIONS

8.1 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 ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis).

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

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

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest

dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study.

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

Pregnancy-Nonteratogenic Effects

Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*].

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1—2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [*see Dosage and Administration (2.1)*]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Lexapro is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Lexapro has not been established in pediatric patients (less than 12 years of age) with Major Depressive Disorder. Safety and effectiveness of Lexapro has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder [*see Clinical Studies (14.1)*]. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.

Safety and effectiveness of Lexapro has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder.

8.5 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.

SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Hyponatremia (5.6)*].

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 (12.3)*]. 10 mg/day is the recommended dose for elderly patients [*see Dosage and Administration (2.3)*].

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.

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse and Dependence

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).

10 OVERDOSAGE

10.1 Human Experience

In clinical trials of escitalopram, there were reports of escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. During the postmarketing evaluation of escitalopram, Lexapro overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported.

Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

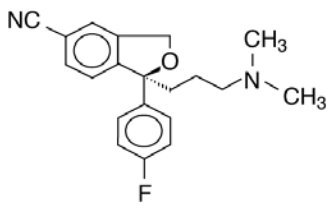
10.2 Management of Overdose

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.

11 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-(dimethyl-amino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula:



•$C_2H_2O_4$

The molecular formula is $C_{20}H_{21}FN_{2O}$ • $C_2H_2O_4$ and the molecular weight is 414.40.

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of

escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

Absorption and Distribution

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

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

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

Metabolism and Elimination

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

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

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

Population Subgroups

Age

Adolescents - In a single dose study of 10 mg escitalopram, AUC of escitalopram decreased by 19%, and C_{max} increased by 26% in healthy adolescent subjects (12 to 17 years of age) compared to adults. Following multiple dosing of 40 mg/day citalopram, escitalopram elimination half-life, steady-state C_{max} and AUC were similar in patients with MDD (12 to 17 years of age) compared to adult patients. No adjustment of dosage is needed in adolescent patients.

Elderly - Escitalopram pharmacokinetics in subjects ≥ 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients [*see Dosage and Administration (2.3)*].

Gender - Based on data from single- and multiple-dose studies measuring escitalopram in elderly, young adults, and adolescents, no dosage adjustment on the basis of gender is needed.

Reduced hepatic function - Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is the recommended dose of escitalopram for most hepatically impaired patients [*see Dosage and Administration (2.3)*].

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

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on CYP3A4, -1A2, -2C9, -2C19, and -2E1. Based on *in vitro* data, escitalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. While *in vivo* data to address this question are limited, results from drug interaction studies suggest that escitalopram, at a dose of 20 mg, has no 3A4 inhibitory effect and a modest 2D6 inhibitory effect. See *Drug Interactions (7.18)* for more detailed information on available drug interaction data.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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.

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

Adolescents

The efficacy of Lexapro as an acute treatment for major depressive disorder in adolescent patients was established in an 8-week, flexible-dose, placebo-controlled study that compared Lexapro 10-20 mg/day to placebo in outpatients 12 to 17 years of age inclusive who met DSM-IV criteria for major depressive disorder. The primary outcome was change from baseline to endpoint in the

Children's Depression Rating Scale - Revised (CDRS-R). In this study, Lexapro showed statistically significant greater mean improvement compared to placebo on the CDRS-R.

The efficacy of Lexapro in the acute treatment of major depressive disorder in adolescents was established, in part, on the basis of extrapolation from the 8-week, flexible-dose, placebo-controlled study with racemic citalopram 20-40 mg/day. In this outpatient study in children and adolescents 7 to 17 years of age who met DSM-IV criteria for major depressive disorder, citalopram treatment showed statistically significant greater mean improvement from baseline, compared to placebo, on the CDRS-R; the positive results for this trial largely came from the adolescent subgroup.

Two additional flexible-dose, placebo-controlled MDD studies (one Lexapro study in patients ages 7 to 17 and one citalopram study in adolescents) did not demonstrate efficacy.

Although maintenance efficacy in adolescent patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.

Adults

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 statistically significant 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 statistically significant 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 statistically significant greater mean improvement compared to placebo on the MADRS.

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

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

14.2 Generalized Anxiety Disorder

The efficacy of Lexapro in the acute 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 adult outpatients between 18 and 80 years of age who met DSM-IV criteria for GAD. In all three studies, Lexapro showed statistically significant 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Tablets:

5 mg Tablets:
Bottle of 100 NDC # 0456-2005-01
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 100 NDC # 0456-2010-01
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 100 NDC # 0456-2020-01
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".

16.2 Oral Solution:

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide

17.1 Information for Patients

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

General Information about Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Lexapro and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for Lexapro. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Lexapro.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [*see Warnings and Precautions (5.1)*].

Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of **Lexapro** and triptans, tramadol or other serotonergic agents [*see Warnings and Precautions (5.2)*].

Abnormal Bleeding

Patients should be cautioned about the concomitant use of Lexapro and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding [*see Warnings and Precautions (5.7)*].

Concomitant Medications

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

Continuing the Therapy Prescribed

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

Interference with Psychomotor Performance

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.

Alcohol

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.

Pregnancy and Breast Feeding

Patients should be advised to notify their physician if they

- become pregnant or intend to become pregnant during therapy.
- are breastfeeding an infant.

Need for Comprehensive Treatment Program

Lexapro is indicated as an integral part of a total treatment program for MDD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all adolescents with this syndrome. Safety and effectiveness of Lexapro in MDD has not been established in pediatrics patients less than 12 years of age. Antidepressants are not intended for use in the adolescent who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe antidepressant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

17.2 FDA-Approved Medication Guide

MEDICATION GUIDE
Lexapro® (escitalopram oxalate) Tablets/Oral Solution

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

• all risks and benefits of treatment with antidepressant medicines
• all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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Rev. 01/09

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

MEDICAL REVIEW(S)

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 19, 2009

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Approval Action for Lexapro (escitalopram) tablets and solution as monotherapy for the acute and maintenance treatment of major depressive disorder (MDD) in adolescent patients

TO: File NDA 21-323_S-030/031 and NDA 21-365_S-021/022
[Note: This overview should be filed with the 5-22-08 original submissions of these supplements.]

1.0 BACKGROUND

Lexapro (escitalopram), the S-enantiomer of citalopram, is an SSRI that is approved (1) as monotherapy for the acute and maintenance treatment of MDD in adults, and (2) as monotherapy for the acute treatment of GAD in adults. This supplement provides data in support of claims for Lexapro for acute monotherapy and maintenance monotherapy of MDD in adolescent patients. These studies were conducted under IND 58,380. There is currently only one other drug approved for the treatment of pediatric MDD, i.e., fluoxetine.

The sponsor's proposed dose range for Lexapro in adolescent MDD is 10 to 20 mg/day.

The primary review of the efficacy and safety data was done by Roberta Glass, M.D., from the clinical group. George Kordzakhia, Ph.D., from the biometrics group, also reviewed the efficacy data. These supplements included labeling for Lexapro in PLR format for the first time. This new labeling format required review by all disciplines. In addition, this revised labeling was reviewed by the Maternal Health Team (MHT).

We decided not to take these applications to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

Lexapro is an approved product, and there were no CMC issues that required review as part of this supplement, except for an environmental assessment for which a request for categorical exclusion was made and accepted.

3.0 PHARMACOLOGY

Lexapro is an approved product. There were no pharm/tox issues that required review as part of these supplements, other than for labeling in the PLR format.

4.0 BIOPHARMACEUTICS

Lexapro is an approved product. The sponsor included data from 3 pharmacokinetic studies in pediatric patients as part of these supplements, and these data were reviewed by Andre Jackson from OCP. They also reviewed the sponsor's proposed label. OCP concluded that no dose adjustment is needed in adolescents, compared to adults, and had no comment on the sponsor's proposed label.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

The sponsor needed 2 positive short-term efficacy trials to support a claim for pediatric MDD, and in prior discussions, we had agreed that it would be sufficient to provide data from 1 positive study with Lexapro. We agreed to extrapolate on the basis of a previously reviewed positive study with citalopram (Study CIT-MD-18).

Overall, the sponsor submitted data from 3 Lexapro studies pertinent to its new claims in adolescent MDD, including from 2 short-term studies (Studies SCT-MD-32 and SCT-MD-15) and from a double-blind, controlled extension study (Study SCT-MD-32A). They were seeking both an acute and a maintenance claim in adolescent MDD. As noted, they also referenced Study CIT-MD-18, and I will also briefly summarize a fifth short-term citalopram study, i.e., 94404. All of these trials were flexible-dose and none included an active control arm.

Acute Monotherapy Studies

-Study SCT-MD-32: This was a randomized, double-blind, parallel group, placebo-controlled, flexible-dose (escitalopram 10-20 mg/day), 8-week trial in adolescent outpatients (ages 12-17)

meeting DSM-IV criteria for MDD. The primary endpoint was change from baseline to endpoint on the CDRS-R total score. Escitalopram was statistically significantly superior to placebo (Pbo: -18.4; escit: -22.4; p=0.022).
-Study CIT-MD-18: This was a randomized, double-blind, parallel group, placebo-controlled, flexible-dose (citalopram 20-40 mg/day), 8-week trial in pediatric outpatients (ages 7-17) meeting DSM-IV criteria for MDD. The primary endpoint was change from baseline to endpoint on the CDRS-R total score. Citalopram was statistically significantly superior to placebo (Pbo: -16.5; cit: -21.7; p=0.038). While this study was positive overall, the effect size was greater for the adolescent subgroup compared to the child subgroup (7.2 units on the CDRS-R for adolescents vs 3.8 for children).
-Study SCT-MD-15: This was a randomized, double-blind, parallel group, placebo-controlled, flexible-dose (escitalopram 10-20 mg/day), 8-week trial in pediatric outpatients (ages 6-17) meeting DSM-IV criteria for MDD. The primary endpoint was change from baseline to endpoint on the CDRS-R total score. Escitalopram was not statistically significantly superior to placebo (Pbo: -20.3; escit: -20.9; p=0.31). The adolescent sample in this study was slightly larger (n=160; p=0.233) than the child sample (n=104; p=0.875).
-Study 94404: This was a randomized, double-blind, parallel group, placebo-controlled, flexible-dose (citalopram 20-40 mg/day), 8-week trial in adolescent outpatients meeting DSM-IV criteria for MDD. The primary endpoint was change from baseline to endpoint on the Kiddie-SADS_P total score. Citalopram was not statistically significantly superior to placebo. Thus, this was another negative study.

Maintenance Study (SCT-MD-32A)

This was not a randomized withdrawal study, as is usually the case with a study proposed as a basis for a maintenance claim. Rather, Study 32A was a double-blind, placebo-controlled 16-week extension of responders from Study 32. As such, it violated randomization, and we do not consider it interpretable. Thus, I will not comment further on the results from this study.

5.1.2 Comment on Other Important Clinical Issues Regarding Efficacy

Evidence Bearing on the Question of Dose/Response for Efficacy

These were all flexible-dose studies, thus, there is no basis for assessing dose response for efficacy.

Key Secondary Endpoints

CGI was prespecified as a key secondary endpoint in both studies 32 and 18. Although escitalopram was superior to placebo on the CGI in Study 32 (p=0.008), this was not the case for Study 18 (b) (4)

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of age, gender, and race. There was no indication of any difference in effectiveness based on these analyses.

Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in change from baseline on the CDRS-R were similar to effect sizes seen in other positive pediatric MDD trials.

Duration of Treatment

Although we do not consider Study 32A to be a reasonable basis for assessing maintenance efficacy, we have been willing to extrapolate from adult maintenance data when both acute and maintenance efficacy have been established in adults and acute efficacy has been established. I am willing to make such an extrapolation to pediatric patients in this case as well.

PMR Study in Children with MDD

Although the sponsor has provided some data from the 7-11 age group, I do not feel they have adequately explored efficacy in this subgroup. The effect size in the 7-11 age subgroup in Study 18 is actually about the same as that seen in the positive escitalopram study (32), but the sample size may have been too small to show statistical significance. It is very likely that patients in the 7-11 age group will be treated with Lexapro, even in the absence of sufficient data. We cannot require an efficacy study in the 7-11 age group under PREA or under FDAAA. We discussed this issue with the sponsor, and they were not willing to commit to another efficacy study in children. However, they do plan to conduct an open label safety study in children with MDD.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support a claim for the acute treatment of MDD in adolescent patients, and I am willing to extrapolate maintenance efficacy for adults with this condition to adolescent depression.

5.2 Safety Data

There were no unexpected or unusual safety findings that would impact on labeling or an approval action for this application.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling and we have reached agreement with them on final labeling.

6.0 WORLD LITERATURE

The literature review did not reveal any unexpected or unusual safety findings that would impact on labeling or on an approval action for this application.

7.0 FOREIGN REGULATORY ACTIONS

Lexapro is not approved for any pediatric indications in any other countries.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

These applications were not take to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at two sites that enrolled patients from study 32. The data from these sites were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

As noted, we reached agreement on final labeling.

11.0 CONCLUSIONS AND RECOMMENDATIONS

The sponsor has submitted sufficient data to support the conclusion that Lexapro is effective as acute monotherapy in the treatment of adolescent MDD. We are able to extrapolate maintenance efficacy to pediatric patients from positive data in adults with MDD. The safety profile appears to be similar to that observed with this drug in adults. We have reached agreement on final labeling, and I will issue an approval letter.

cc:
Orig NDAs 22-323_S-030/031/NDA 21-365_S-021_022
HFD-130
HFD-130/TLaughren/MMathis/NKhin/RGlass/RGrewal

DOC: Laughren_NDA21323_S-30_31_Lexapro_Peds_MDD_AP Memo.doc

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

/s/

Thomas Laughren
3/19/2009 10:56:02 AM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: February 17, 2009

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: NDA 21-323/SE5-030/031 (tablets)
NDA 21-365/SE5-021/022 (oral solution)
(This overview should be filed with the 05-22-2008 submission.)

SUBJECT: Recommendation of Approval Action for Lexapro (escitalopram) for the Acute and Maintenance Treatment of Major Depressive Disorder (MDD) in Adolescents

1. BACKGROUND

Lexapro (escitalopram), the S-enantiomer of the racemic citalopram, is a serotonin reuptake inhibitor (SSRI). It is approved in the U.S. since 2002, for the treatment of major depressive disorder (MDD) in adults at doses up to 20 mg per day. It is also approved for the treatment of generalized anxiety disorder in adults. The recommended dose is 10 mg daily with dose can be increased to 20 mg/day. Escitalopram tablets are available in 5, 10 and 20 mg strengths. It is also available in oral solution form, 5 mg/ml.

Currently, Prozac (fluoxetine) is approved fro use the pediatric population for the MDD indication. Both Celexa (citalopram) and Lexapro (escitalopram) are approved for acute and maintenance treatment of MDD in adults.

The Agency has received sponsor's submission of the above referenced supplemental NDAs on 5/23/08. The applications included the efficacy and safety results from a positive short-term study with escitalopram (Study SCT-MD-32) in adolescents with MDD. They also included results from Study SCT-MD-32A, a 16-week extension study.

This set of supplemental NDAs has been reviewed by Roberta Glass, M.D., Medical Officer, DPP (review dated 01/29/2009) and George Kordzakhia, Ph.D., Statistical Reviewer, from the Office of Biostatistics (review dated 01/28/2009). An Environmental Assessment Review was conducted by Nallaperum Chidambaram, Ph.D., Chemist, ONDQA (memo dated 09/12/2008).

In this submission, the sponsor has made conversion of the Lexapro labeling to new PLR format. Each discipline was asked to provide any PLR labeling comments during the review cycle. In addition, this set of supplements was chosen by the Maternal Health Team (MHT) from OND as part of their pilot projects for PLR labels and provided some labeling recommendations regarding section 8.1 (Pregnancy) and 8.3 (Nursing Mothers) (in review dated 1/29/2009 by Jeanine Best).

2.0 CHEMISTRY

No new CMC information submitted in this NDA supplement except environmental assessment issues. The applicant had claimed categorical exclusion from submitting an EA document and such claim was found acceptable. In addition, there are no further changes to the proposed PLR labeling from a CMC perspective per Dr. Nallaperum Chidambaram, ONDQA, in his email dated 2/10/2009.

3.0 PHARMACOLOGY/TOXICOLOGY

No new pharmacology/toxicology issues submitted in this supplemental NDA. Dr. Barry Rosloff, Supervisory Pharmacologist, provided some minor PLR labeling edits for the pharmacology/ toxicology sections. He also reviewed PLR labeling recommendations from the MHT. Dr. Rosloff noted that MHT has recommended several changes to section 8.1 (Pregnancy). As suggested by MHT, it was acceptable to have an introductory paragraph followed by an Animal Data section in the PLR label, but it was unacceptable to him that numerous editorial changes to the description of the animal data should be made. (b) (4)

4.0 CLINICAL PHARMACOLOGY

There was no new OCP issues submitted that would require a review. OCP will be providing PLR labeling comments. At the time completing this memo, I have not received their labeling comments yet.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

To fulfill the requirement of positive results from two placebo-controlled studies to support efficacy of pediatric MDD for escitalopram, the division has agreed to accept one positive pivotal study in citalopram Study CIT-MD-18 (Study 18) and one positive study in escitalopram Study SCT-MD-32 (Study 32). Because Study 32 enrolled adolescents only, and the positive efficacy results of Study 18 derived primarily from the adolescent treatment group, the sponsor's intended indication claim is for treatment of MDD in adolescents.

In this review cycle, our review of efficacy was focused on the positive results from one placebo-controlled short-term study (study SCT-MD-32) in our evaluation of the efficacy and safety of escitalopram in the acute treatment of MDD in adolescents.

Study 32 is an 8 week, double-blind, placebo-controlled, flexible dose (escitalopram 10-20 mg/d) study in adolescents (age 12-17 yrs) with MDD. The clinical and statistical reviews covered the

details of study design and findings in this study. I will discuss the efficacy data from this study in the subsection 5.1.2.1 below.

As noted by both Drs. Glass and Kordzakhia in their reviews, I concur that the Study SCT-MD-32 A (hereafter referred as study 32A)**,** a 16 week extension study, would give uninterpretable results due to design flaws. It should not be used to support maintenance efficacy claim.

Study 18 is an 8 week, double-blind, placebo-controlled, flexible dose (citalopram 20-40 mg/d) study in children (7-11 yrs) and adolescents (12-17 yrs). I would refer to the clinical review by Dr. Earl Hearst dated 9/12/02 and a memorandum by Dr. Thomas Laughren dated 9/16/02 regarding their reviews of materials submitted under supplemental NDA for citalopram on 04/18/2002. I will briefly summarize their interpretation of results from the Study 18 in section 5.1.2.3 below.

Two other studies were considered negative and they were not reviewed in detail for efficacy: Study SCT-MD-15 (Study 15), an 8 week, placebo-controlled, flexible dose (escitalopram 10-20 mg/day) study in children and adolescents; and Study 94404, a 12 week, double-blind, placebo-controlled, flexible-dose study (citalopram 10-40 mg/day) in adolescents with MDD.

5.1.2 Summary of Study Pertinent to Efficacy Claim

5.1.2.1 Study SCT-MD-32

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose (escitalopram 10-20 mg/day) study of the safety and efficacy of escitalopram in the treatment of adolescent patients (12-17 years of age) with a DSM-IV diagnosis of MDD.

The study consisted of a 2-week screening period, including single-blind placebo lead-in during the second week, followed by 8 weeks of double-blind treatment. At the end of the single-blind period, eligible patients were randomized 1:1 to one of two double-blind treatment groups (escitalopram or placebo). The escitalopram dosage was 10 mg/day for the first three weeks of double-blind treatment. The dosage could be increased to 20 mg/day by the investigator at the end of Treatment Week 3 (Visit 6) or Treatment Week 4 (Visit 7). Patients who completed the 8-week double-blind treatment period were eligible to enter a 1-week double-blind down-taper period or to continue in an extension study for additional 16 weeks (Study SCT-MD-32A).

This study was conducted at 40 study centers in the United States (US). A total of 584 patients were screened for eligibility; 316 patients were randomized to receive either study drug or placebo and 311 patients had at least one post-baseline CDRS-R assessment (ITT Population). A total of 133 (84.2%) placebo patients and 126 (79.7%) escitalopram patients completed 8 weeks of double-blind treatment, and 202 patients (100 placebo, 102 escitalopram) continued into the extension study, SCT-MD-32A. There were 94 subjects discontinued from the study: 52 (37.1%) in the escitalopram and 42 (30%) in the placebo group. Reasons for discontinuation included lack of therapeutic response [5 subjects (3.2%) in each group]; adverse events [4 subjects (2.5%) in escitalopram and 1 (0.6%)]; withdrawal of consent, lost to follow up, protocol violations and others.

The mean patient age was 14.6 years; majority was Caucasian (75%) and females (59%). There were no statistically significant differences between the two treatment groups with respect to demographic characteristics. However, the sponsor stated that there were statistically significant

differences in CDRS-R total score and CGI-S at baseline between the two treatment groups with higher depression severity in the escitalopram group.

All efficacy analyses were performed on the ITT Population. All primary and secondary efficacy analyses were performed using the LOCF approach. The between–treatment group comparison was performed using a two-way analysis of covariance (ANCOVA) model with treatment group and study center as factors and the baseline score as a covariate. A sensitivity analysis for the primary efficacy parameter was performed using the mixed-effects model for repeated measures (MMRM) methodology based on the observed post-baseline longitudinal data. The model included study center, treatment group, visit, and treatment group-by-visit interaction as factors and baseline value as covariate. The primary efficacy parameter was the change from baseline to Week 8 in CDRS-R total score. The key secondary efficacy parameter was the CGI-I score.

Dr. Kordzakhia confirmed sponsor's primary efficacy analysis. As can be seen in table 1 below, the change from baseline to Week 8 in the escitalopram group was statistically significantly greater than that in the placebo group. As noted in his statistical review, the findings from the sensitivity analysis, MMRM, support the primary efficacy results.

Table 1: Primary Efficacy Results on Change from baseline in CDRS Total Scores at endpoint (LOCF; ITT population)

Treatment Groups (Total Number =311)	Mean Baseline total CDRS (SD)	LS mean Change from Baseline Mean at endpoint	Placebo adjusted difference (95% CI); p-values (drug vs. placebo)
Escitalopram (N=154)	57.6 (0.7)	-22.4 (1.1)	-3.4 (-6.2, -0.5); p=0.022
Placebo (N=157)	56 (0.7)	-18.4 (1.1)	

Comment: Both Drs. Glass and Kordzakhia considered this a positive study for escitalopram, and I agree with them.

5.1.2.2 Study SCT-MD-32A

As noted by Dr. Glass in her review, Study 32A was originally designed as a 24 week, flexible-dose, open label extension study. After the study began and patient data was collected, the protocol was amended several times to evolve into a double blind, placebo controlled, 16 week extension study. The study design did not allow re-randomization of patient treatment assignment at the beginning of Study 32A after completing Study 32. The study showed almost 75% drop out rate for both treatment groups. I agree with both Dr. Glass and Kordzakhia's comments that the maintenance effect in this study would be confounded with the acute effect. The data for this study was considered uninterpretable.

5.1.2.3 Study CIT-MD-18

Study 18 is an 8 week, randomized, double-blind, placebo-controlled, flexible dose citalopram (20-40 mg/day) study conducted in 160 pediatric patients (aged 7-17) diagnosed with MDD. The treatment groups are stratified for age group (children: 7-11 and adolescents: 12-17). The primary

efficacy variable is the change from baseline to 8 weeks comparing the placebo and citalopram groups on the Children's Depression Rating Scale-Revised (CDRS-R).

A total of 83 children (age 7-11) entered the study; 66 completed the study [citalopram n=36 (80%); placebo n=30/38 (79%)]. A total of 91 adolescents (age 12-17) entered the study; 72 completed the study [citalopram n=35 (79.5%); placebo n=37/47 (79%)]. The mean age in both treatment groups is 12 y.o. with the majority of patient being female (53% for citalopram and 54 % for placebo) and Caucasian (81% and 73%, respectively).

The study was positive for the primary efficacy variable of change from baseline of the CDRS-R total score: citalopram -21.7 $\pm$ 1.6; placebo -16.5 $\pm$ 1.6 (p=0.038). Please see Table 2 in section 5.1.3 regarding summary of primary efficacy results by age group for Study CIT-MD-18 (LOCF data extracted from Dr. Laughren's memo dated 9/16/2002). There seemed a greater improvement for the adolescent group than the children group when comparing the differences to placebo. It also appears that the positive results for this trial were coming largely from the adolescent subgroup.

5.1.2.4 Study SCT-MD-15

This study was a double blind, placebo controlled, 8-week, flexible dose (escitalopram 10-20 mg/day) study in children and adolescents (6-17 yrs) with MDD. This study was conducted at 25 study centers in the United States (US). 264 patients were randomized to receive either escitalopram (n=131) or placebo (n=133); 217 completed the study: escitalopram (n=102), placebo (n=115). Mean age was 12.3 yrs with a subset of adolescents randomized to placebo was 81 and the escitalopram group was 79. The study results did not show any statistical significance for the primary efficacy variable of change from baseline of the CDRS-R total score at week 8: escitalopram -20.3 $\pm$ 1.3; placebo -20.9 $\pm$ 1.2; p=0.084. The study was considered a negative study.

5.1.2.5 Study 94404

This study was a double-blind, placebo-controlled, 12 week, flexible dose (citalopram 10-40 mg/day) study in adolescents with MDD. This study was conducted at 31 international sites. The primary efficacy variable was change from baseline of Kiddie-SADS-P at week 8. This study was also considered a negative study.

5.1.3 Comments on Other Important Clinical Issues

Subgroup analyses on treatment effect

Exploratory subgroup analyses were performed in order to detect subgroup interactions on the basis of gender (M, F), and race (White, African American, others) on the primary efficacy variable, change from baseline in CDRS-total scores at week 8. For all subgroups (except for African American, comprised of a small number [N=24] of patients, did not demonstrate any improvement), the treatment effect appeared to be numerically in favor of escitalopram when compared with placebo in study SCT-MD-32.

As noted before in Dr. Hearst's clinical review and Dr. Laughren's team leader memo, in study 18, subgroup analysis based on age (children: 7-11; adolescents: 12-17 yrs) showed that there was a greater improvement for the adolescents than the children when comparing the differences to

placebo. It appeared that the positive results for this trial were coming largely from the adolescent subgroup (Table 2).

Table 2: Summary of primary efficacy results by age group for Study CIT-MD-18 - LOCF (data extracted from Dr. Laughren's memo dated 9/16/2002)

Age Group	Treatment Groups	Mean baseline CDRS-R Total Score	Mean change from baseline CDRS-R
Children (N=83)	Citalopram (N=45) Placebo (N=38)	60.0 56.8	-20.9 -17.1
Adolescents (N=91)	Citalopram (N=44) Placebo (N=47)	57.5 58.6	-22.6 -15.4

Given these findings, I concur with Dr. Glass that we should ask the sponsor to conduct additional short-term efficacy study in children (age 6-12 yrs) as part of Phase 4 post-marketing requirements. MDD can be reliably diagnosed in this younger age population.

Key secondary efficacy variable

The key secondary efficacy variable established is the CGI-I, a clinician-rated instrument used to rate the total improvement or worsening in a patient's mental illness, based on the Investigator's clinical opinion. Study 32 showed statistically significant difference in change from baseline in favor of escitalopram treatment, compared to placebo using the ANCOVA model for the CGI-I (p=0.008); however, Study 18 with citalopram did not demonstrate statistical significance for this efficacy variable.

(b) (4)

Dose Response Relationship

Study 32 is a flexible dose study of escitalopram 10-20 mg/day. No adequate studies have been conducted to explore dose-response relationship in this patient population.

Duration of Treatment

Although the sponsor intends to have a maintenance claim based on results from the longer-term extension phase study 32A, we have decided that study 32A cannot be used for maintenance claim as it would give uninterpretable results due to design flaws. However, the Division's current policy would allow for maintenance claim in pediatrics based on extrapolation from adult MDD maintenance claim once acute pediatric treatment is established as efficacious.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analysis of study 32 supported the efficacy claim of escitalopram in the acute treatment of MDD in adolescents. Based on prior clinical review by Dr. Hearst and Dr. Laughren's memo, we should be able to count on positive efficacy results from citalopram study 18

in the same aged population for acute treatment of MDD. Maintenance claim in treatment of MDD for the adolescent population is supported by extrapolation from adult data.

5.2 Safety Data

5.2.1 Safety Database

Dr. Glass' safety review of this supplemental NDA included data from escitalopram studies in patients with MDD with the safety data base cut-off date of 12/31/2007. The escitalopram safety data base for treatment of adolescents with MDD includes the following: Study 32, 8 week adolescents (12-17 yrs) study using flexible dose escitalopram (10-20 mg/d) (n=157) vs. placebo (n=155); Study 32A, a longer term, 16 week extension study (24 week total); and Study 15, 8 week flexible dose escitalopram (10-20 mg/d) (n=131 includes 79 adolescents) study in pediatric (6-17 yrs.) patients diagnosed with MDD placebo (n=133 includes 81 adolescents).

The safety update covered the period of 01/08 to 05/2008 regarding the sponsor's review of spontaneous post-marketing adverse events reports.

(b) (4)

A total of 988 pediatric patients received ≥1 dose of study drug; of these, 764 patients were between ages 12-17 yrs and 36 patients aged 18 yrs The sponsor counted a total of 800 adolescent patients in the escitalopram/citalopram safety data base: escitalopram n=234; citalopram n=169 and placebo n=387. A total of 210 patients (181 adolescents) received escitalopram for at least 8 weeks, and 53 patients (all adolescents) received escitalopram for at least 24 weeks; 211 patients (154 adolescents) received citalopram for at least 8 weeks, and 66 patients (30 adolescents) received citalopram for at least 24 weeks. The sponsor concludes that the escitalopram/citalopram safety data base included 83 adolescents who were exposed for up to 24 weeks of escitalopram or citalopram. Doses for escitalopram are either 10 or 20 mg daily. Of the 154 intent-to-treat escitalopram patients in Study 32, 54 patients received 10 mg on their last visit, and 100 patients received 20 mg on their last visit. Overall exposure (in patient years) was 58.7 (all aged groups in 286 escitalopram treated patients) and 51.3 (in 234 adolescents treated with escitalopram).

There was no death reported in the escitalopram safety database review for this submission. Serious adverse events were available from this double-blind phase. In those subjects who experienced SAE, the events included suicidalty (ideation and attempts) and aggravation of depression, and they were identified in both placebo and escitolopram treated groups. The incidence of premature withdrawal was greater in the escitopram group (4.3%) compared to the placebo group (1.3%). The most common AE in dropouts in the escitalopram included insomnia, self injury, fatigue and restlessness.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). Based on the information provided by the sponsor in this application, no AEs terms would meet this definition from the acute studies; UTI from the longer term study. The common AE occurring with greater frequency in the escitalopram compared to placebo in acute studies included headaches, abdominal pain, nausea and insomnia; diarrhea in the longer term study.

5.2.2.2 Vital Signs and Growth Data

In the short term studies (15 and 32) weekly vital sign monitoring included sitting pulse, blood pressure, and weight. Height was recorded at baseline and at study end or early termination. In the longer term study (32A), sitting pulse, blood pressure and weight were measured weekly for the first 5 weeks and then monthly. Orthostasis was assessed in Studies 32 and 32A at baseline and the end of Weeks 1, 6, 10, 12, and 24. There were no clinically significant vital sign change differences (blood pressure and pulse) comparing the placebo and escitalopram groups.

Regarding growth assessment in the pediatric population as determined by use of a z-score (defined by the number of standard deviations from the population mean for a specific subject's weight or height given their age and sex), the sponsor stated that the z-score changes appeared to be similar between treatment groups, indicating that escitalopram did not appear to have an identifiable effect on height and weight change in the study adolescent population. Dr. Kordzakhia has confirmed the sponsor's findings in his statistical review.

5.2.2.3 ECG Data

There were no dropouts due to ECG abnormalities. As stated by Dr. Glass in her clinical review, there were two patients (0091505 and 0303213) with an increased QTc prolongation of > 60 msec; no placebo patients have a clinically significant increase in QTc. The escitalopram patients with an increase from baseline to endpoint in QTc during escitalopram treatment (without significant increase in heart rate): QTcF 2.7$\pm$15.5 ms vs. -0.1$\pm$15.4 in placebo.

The sponsor is conducting a thorough QT study to better characterize the QTc effect of this drug. As proposed by the Agency, the sponsor submitted the protocol, a six-sequence, three-period, cross-study using moxifloxacin as control; and the Agency's QT-IRT had reviewed and provided comments to the sponsor regarding the study design in September, 2008. The Division intends to let current label stand until results from the QT study are received and can be reviewed.

5.2.2.4 Laboratory Tests

There were no significant differences between the escitalopram and placebo groups in mean changes from baseline to endpoint in all laboratory values tested. It was noted that the mean increase for AST was higher in the escitalopram group (0.9$\pm$7 U/L) than in the placebo group (-0.1 $\pm$8.6 U/L).

5.2.2.5 Suicidality Analysis

The sponsor's analysis based on instruments/scales (the Modified Columbia-Suicide Severity Rating Scale and the Suicide Ideation Questionnaire-Junior High School Version) and the incidence of treatment emergent AE potentially associated with suicidal behavior in the escitalopram adolescent safety database was discussed by Dr. Glass in her clinical review, section 7.1.6.

Current escitalopram label contains the standard class suicidality language in the Boxed Warning and the Warnings/Precautions section. The sponsor proposes to use the same language in the PLR label.

5.2.3 Conclusion Regarding Safety Data

Overall, this supplemental NDA submission revealed no new or specific safety concerns. We should continue to monitor and follow up on any post-marketing safety issues with this drug.

6.0 WORLD LITERATURE

The sponsor has provided a literature review in this submission. Based on Dr. Glass' review, the submitted materials indicated some unusual adverse events including tics, EPS, dystonia, oculogyri crisis, Rabbit Syndrome and enuresis. Both Dr. Glass and the sponsor did not raise any specific concerns regarding these AEs with this drug at this time. We should continue to monitor these findings in post-marketing reports for any unconfounding cases.

7.0 FOREIGN REGULATORY ACTION

The sponsor reported that there is no application pending or approved for escitalopram in either pediatric MDD or other pediatric indications in any countries outside the US.

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 study sites (Northwest CRC in Bellevue, WA, and PCSD-Feighner Research in San Diego, CA) participated in study 32. Based on our communication with DSI, DSI did not find any major violations from these two sites that would compromise data integrity. DSI clinical inspection summary is pending.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

This submission contains revised labeling in a new PLR format. We plan to incorporate part of the labeling changes proposed by the MHT, and also, the SEALD team's recommendation when received. I note Dr. Glass' recommendation to include a section in the label entitled "Need for Comprehensive Treatment Program" modeled after the section for stimulant use in ADHD in highlighting drug treatment is one aspect of the effective MDD therapies available for adolescents

with MDD. The sponsor's proposed language in this submission should be modified. All these labeling changes will be negotiated with the sponsor. A copy of final labeling should be included in the action letter.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to demonstrate that escitalopram is effective and reasonably safe in acute treatment of MDD in adolescents. We should consider for maintenance claim in treatment of MDD for the adolescent population by extrapolation from adult data. I recommend we consider approval of this set of NDA supplements provided that we reach an agreement with the sponsor regarding the language in the labeling. We should ask the sponsor to conduct additional short-term efficacy study in children (6-12 yrs) with MDD as part of post-marketing requirement.

cc: HFD-130/Laughren/Mathis/Glass/Grewal

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/s/

Ni Aye Khin

2/17/2009 11:03:00 AM

MEDICAL OFFICER

CLINICAL REVIEW

Application Type /Submission #:	NDA 21-323/S-30 (tablets) [redacted] (b) (4) (oral solution)
Submission Code	SE5
Letter Date	5/22/08
Stamp Date	5/23/08
PDUFA Goal Date	3/23/09
Reviewer Name	Roberta Glass, M.D.
Review Completion Date	1/29/09
Established Name	Escitalopram
Trade Name	Lexapro
Therapeutic Class	Selective Serotonin Reuptake Inhibitor (SSRI)
Applicant	Forest Laboratories, Inc.
Priority Designation	S
Formulation	Tablets (5 mg, 10 mg, and 20 mg) and Oral Solution (5 mg/mL)
Dosing Regimen	10 to 20 mg/day
Indication	Major depressive disorder (MDD)
Intended Population	Adolescents (12-17 years old)

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that escitalopram be approved for the indication of MDD in the adolescent population at an initial dose of 10 mg qd; this dose may be sufficient for clinical improvement. Some patients may benefit from a dose increase to 20 mg qd, but this upward titration should occur only after a sufficient trial at the lower dose of 10 mg. The labeling may state that safety and efficacy of doses 10 mg and 20 mg escitalopram are demonstrated in the adolescent population.

Because escitalopram has been shown to be effective in the acute treatment of adolescent MDD, current policy allows for the extrapolation of the adult MDD maintenance claim/data to support a maintenance claim in the adolescent population.

It is recommended that any pediatric claim be restricted to adolescents (12-17) and not include children (6-11), because the escitalopram pivotal study includes adolescents only. Even though the pivotal citalopram study supporting this efficacy claim includes children (7-11), the efficacy results strongly suggest that the adolescent group demonstrates a greater benefit of treatment for MDD than the younger aged children. The negative study in escitalopram, which includes both children and adolescents, also demonstrates a greater response in adolescents than children.

Finally, it is recommended that the labeling include language that encourages clinicians to focus on a comprehensive treatment plan of which drug treatment is only one aspect of the effective treatment of MDD in adolescents.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

It is important that the sponsor continue to monitor treatment emergent suicidality in this very vulnerable population of adolescents suffering with major depressive disorder.

1.2.2 Required Phase 4 Commitments

Because escitalopram will obtain labeling for the adolescent population with MDD, it is likely that clinicians will increase their use in younger children off-label. It would be helpful if the sponsor would power a study to assess the efficacy of escitalopram in this younger population.

It is curious that a subgroup analysis revealed that patients categorized as African American did not demonstrate an improvement in MDD symptoms with escitalopram treatment. This observation and the fact that the escitalopram data base was composed primarily of Caucasians (>70%) would suggest that studying adolescents in varied racial background would offer clinicians better guidance for treatment decisions for individual patients.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Escitalopram, the S-enantiomer of the racemic citalopram, is a selective serotonin reuptake inhibitor (SSRI) marketed in the United States since 2002. Escitalopram is labeled for two indications: 1) the acute and long term treatment of patients with **major depressive disorder (MDD),** and 2) **generalized anxiety disorder (GAD)**; both indications are limited to the **adult** population. This current application proposes to expand the labeling to include **adolescents** for the indication of **MDD.**

To fulfill the requirement of two placebo-controlled studies to support efficacy of pediatric MDD for escitalopram, FDA agrees to accept one positive pivotal study in citalopram (Study 18) and one positive study in escitalopram (Study 32). Because Study 32 is in adolescents only, and the positive efficacy results of Study 18 are primarily in the adolescent treatment group, the recommended pediatric claim is limited to treating MDD in adolescents. Current FDA policy allows for long term pediatric claims based on adult MDD maintenance claim data once acute pediatric treatment is established as efficacious; therefore, the labeling may be eligible for an adolescent MDD maintenance claim based on the extrapolation of adult data.

Study 32 is an 8 week, double-blind, placebo-controlled, adolescent (12-17), flexible dose (10-20 mg/d escitalopram) study. **Study 18** is an 8 week, double-blind, placebo-controlled, flexible dose (citalopram 20-40 mg/d) study in children (7-11) and adolescents (12-17). The following two studies included in this current submission can't be used to support efficacy claims, but did contribute to the escitalopram adolescent safety data base: 1) **Study 15**, an 8 week, placebo-controlled study in children and adolescents has negative results, and 2) **Study 32A,** a 16-24 week extension study has uninterpretable results due to design flaws.

In the **escitalopram** adolescent safety data base (Studies 15 and 32; Study 32A is an extension study of 32), there are 135 females (or 57.7%), and 99 males (42.3%) with a mean age of 14.6 years (± 1.6) exposed to escitalopram. A total of 210 patients (181 adolescents) received **escitalopram** for at least 8 weeks, and 53 patients (all adolescents) received **escitalopram** for at least 24 weeks.

In the **citalopram** pediatric safety data base, 211 patients (154 adolescents) received **c**italopram for at least 8 weeks, and 66 patients (30 adolescents) received **citalopram** for at least 24 weeks. The sponsor concludes that the **escitalopram/citalopram** safety data base includes 83

adolescents (of 119 pediatric patients) who were exposed for up to 24 weeks of **escitalopram** or **citalopram**.

1.3.2 Efficacy

For the primary efficacy variable, the Children's Depression Rating Scale-Revised (CDRS-R), the sponsor demonstrates a statistically significant difference in change from baseline when comparing escitalopram treatment with placebo using the ANCOVA model for both Study 32 (escitalopram: p=0.022) and Study 18 (citalopram: p=0.038).

The key secondary efficacy variable established is the CGI-I, a clinician-rated instrument used to rate the total improvement or worsening in a patient's mental illness, based on the Investigator's clinical opinion. Study 32 (escitalopram) demonstrates statistically significant difference in change from baseline when comparing escitalopram treatment with placebo using the ANCOVA model for the CGI-I (p=0.008); however, Study 18 (citalopram) doesn't demonstrate statistical significance for this efficacy variable.

There are less than 25% of non-Caucasians in the data base; a subgroup analysis conducted by FDA statistician suggests that patients categorized as African American don't demonstrate an improvement in CDRS-R scores with escitalopram treatment.

1.3.3 Safety

The safety data base for this review is primarily limited to the escitalopram in the placebo-controlled studies in adolescents with MDD. Overall, the safety profile in this supplement was consistent with current labeling. Many of the safety concerns that arose with this supplement NDA data base are discussed in the marketed adult labeling for escitalopram.

Of continuing concern is the higher incidence of treatment emergent suicidal gestures/events in the treatment group compared to placebo; this phenomenon is recognized for all anti-depressant use in the pediatric population, and has resulted in a black box warning of suicide in all anti-depressants labeling.

Another phenomenon observed in this safety data base, already recognized in the adult labeling, is a QTc prolongation of 3-4 msec.

1.3.4 Dosing Regimen and Administration

Escitalopram (Lexapro®) is currently labeled for the indication of major depressive disorder and generalized anxiety disorder; both indications are currently **limited to the adult population.**

For **major depressive disorder**, the recommended dose is 10 mg daily at morning or night with or without food; this dose can be titrated up to 20 mg daily after a one week trial of the lower dose. It is noted that in clinical studies, the treatment using 20 mg daily did not show a more significant improvement in treatment than the 10 mg daily use. The labeling supports longer term use of 10 or 20 mg/day for maintenance treatment of major depression, with supporting data of up to 36 weeks treatment exposure.

For **generalized anxiety disorder (GAD)**, the recommended starting dose is 10 mg daily. If the dose is to be increased to 20 mg daily, this should occur after one week at the lower dose. Longer term maintenance treatment for GAD is not supported by the current label.

In the proposed labeling for this submission, the sponsor adds the indication of **major depressive disorder (MDD) in adolescents** aged 12 to 17. The proposed labeling states that the recommended starting dose for escitalopram in adolescents is 10 mg once daily. It recommends that clinical treatment at this lower dose continue for a minimum of 3 weeks prior to titrating upward to 20 mg daily.

1.3.5 Drug-Drug Interactions

The concomitant use of escitalopram with MAOIs is contraindicated. As an SSRI, escitalopram should be used with caution with drugs that affect hemostasis (e.g. NSAIDs, aspirin, warfarin), and other serotonergic drug (e.g. triptans, linezoilid, lithium, tramadol, St. John's Wort, other SSRIs, SNRIs, and typtophan). Caution is also recommended when co-administering escitalopram with any CNS drug or alcohol.

1.3.6 Special Populations

For the special populations of elderly and hepatically impaired patients, the recommended escitalopram dose is 10 mg daily. As with other SSRIs or SNRIs, use of escitalopram in pregnant women during the third trimester may cause neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding; this information has warranted a **Precaution** to use only if the benefits out weigh the risks.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Escitalopram is a selective serotonin reuptake inhibitor (SSRI), and has been marketed in the United States since 2002. It is the S-enantiomer (single isomer) of the racemic derivative citalopram (marketed by Forest as Celexa®). Escitalopram is labeled for two indications: 1) the acute and long term treatment of patients with **major depressive disorder (MDD),** and 2) **generalized anxiety disorder (GAD)**; both indications are limited to the **adult** population. This current application proposes to expand the labeling to include **adolescents** for the indication of **MDD.**

This submission includes two short-term, placebo controlled MDD pediatric studies with the study drug escitalopram; only one of these studies has positive results. The sponsor also presents two short-term, placebo controlled, pediatric studies using the racemic derivative, citalopram, as the study drug. As with escitalopram short-term pediatric studies, only one of the citalopram studies has positive results. (b) (4)

citalopram is not labeled for use in children or adolescents. Because they had conducted the two pediatric studies in the racemic citalopram in response to an FDA issued Written Request, the sponsor received pediatric exclusivity for citalopram and escitalopram in 2002. The sponsor reached an agreement with FDA that a pediatric claim for escitalopram, an isomeric version of citalopram, could be obtained with the support of one positive pediatric study in escitalopram in addition to the one positive study in citalopram. (please see regulatory history Section 2.5 for further details).

In this submission, the sponsor submits longer term escitalopram MDD study in adolescents to support a maintenance claim in this population (Study 32A); however, there are several flaws with this longer term study, deeming the results uninterpretable. More recent regulatory policy allows for a pediatric maintenance claim to be extrapolated from adult data if the following two conditions are met: 1) short term pediatric efficacy is demonstrated in two acute placebo controlled studies, and 2) efficacy has been established for adult longer term treatment.

2.2 Currently Available Treatment for Indications

Currently there is only one drug, fluoxetine (Prozac®), able to demonstrate efficacy in two placebo-controlled studies in the pediatric (children and adolescent) population for the indication of MDD. Fluoxetine is currently the only drug labeled in the U.S. for the treatment of pediatric MDD. There are many anti-depressants marketed in the U.S. that are used off-label to treat MDD in the pediatric population.

2.3 Availability of Proposed Active Ingredient in the United States

Escitalopram (Lexapro®) has been marketed in the United States since 2002. It is currently available in tablet and oral solution formulations.

2.4 Important Issues With Pharmacologically Related Products

Escitalopram shares class label warnings with the SSRIs, SNRIs, and general warnings of anti-depressants. (please refer to the current labeling for more details).

2.5 Pre-submission Regulatory Activity

On April 18, 2002, Forest submitted two pediatric studies assessing the safety and efficacy of citalopram in the use of pediatric MDD in response to an FDA Written Request dated 4/28/99. (b) (4) on July 12, 2002, pediatric exclusivity was awarded to both citalopram (Celexa®) and it's isomer, escitalopram (Lexapro®).

As summarized in the meeting minutes of 10/30/07 (Grewal/Laughren: 11/6/07), a letter from FDA Division of Psychiatric Products (DPP) to Forest Laboratories dated September 23, 2002, confirms that Study CIT-MD-18, a pediatric MDD study with citalopram, is considered positive. In addition, a letter from DPP to Forest Laboratories dated January 31, 2003, confirms that one positive study with racemate citalopram (Study CIT-MD-18) and one positive study with the enantiomer escitalopram (Study SCT-MD- 15) in pediatric patients is sufficient to support a claim for escitalopram use in pediatric patients with MDD.

Study SCT-MD-15 has negative results, and can't be used to support a pediatric MDD claim. In a letter (August 2, 2004), Forest Laboratories requests DPP's input and agreement on potential designs of a proposed new study to support escitalopram use to treat adolescent patients (12-17 years) with MDD. On November 16, 2004, the Division confirms that one additional positive acute treatment study with escitalopram in adolescents, in addition to Study CIT-MD-18, is adequate evidence to support a labeling claim that escitalopram is an effective acute treatment of MDD in adolescents. Thus, Study SCT-MD-32 in adolescent patients was initiated in February 2005.

Also in the meeting minutes of 10/30/07, DPP expresses concern that the protocol design of extension Study 32A can't support a long term claim in pediatric MDD, because patients aren't re-randomized at the beginning of Study 32A (after the completion of Study 32).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new information was submitted in this NDA.

3.2 Animal Pharmacology/Toxicology

No animal studies were submitted with this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of data in this review are the clinical trials submitted by the sponsor (original submission: 5/22/08 and Safety Update: 9/1/08). For other submissions during this review period, please refer to the following EDR link:

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Also considered were the following FDA reviews:

Statistical Review and Evaluation of Escitalopram for MDD; NDA 21-323/ S-030, S-031; 21-365/ S-021, S-022. by George Kordzakhia, Ph.D. (1/28/09).

Pregnancy and Nursing Mothers labeling Lexapro (escitalopram oxylate), NDAs 21-323/S-030,031 and 21-365/S-021,022. by Jeanine Best, MSN, RN, PNP (draft: January, 2009).

Statistical Review and Evaluation for IND 58,380 (escitalopram) of Trial SCT-MD-32A by Yeh-Fong Chen, PhD (10/19/07).

Memorandum: Consult: Suicidality in pediatric clinical trial with paroxetine and other antidepressant drugs by Andrew D. Mosholder, M.D., M.P.H. (9/4/03).

(b) (4)

Review and Evaluation: NDA 20822 (Celexa) by Earl D. Hearst, MD (9/12/02).

4.2 Tables of Clinical Studies

Please refer to the Table 4.2 below for a summary of all studies submitted in this current application.

Study 32 is the only study reviewed for efficacy in this review. Study 18 (review by Dr. Hearst: 9/12/02) supports the escitalopram efficacy claims for the acute treatment MDD in adolescents. The sponsor proposes that Study 32A can support the efficacy claims of maintenance treatment of MDD in the adolescent population; however, due to design flaws, Study 32A is limited to support the safety of escitalopram only. Please refer to the Table 4.2 below for a summary of all studies in the sponsor's current submission.

Table 4.2 Summary table of all studies submitted in current application

STUDY	DESIGN	POPULATION	RESULTS
ESCITALOPRAM PEDIATRIC STUDIES—SHORT TERM PLACEBO CONTROLLED			
Study SCT-MD-32 40 US Centers	8 week double-blind, pbo-controlled, flex dose (10-20 mg/d) escitalopram 1° efficacy variable: CDRS Δ from baseline to 8th week; (CDRS: Children's Depression Rating Scale – Revised). 2° efficacy variable: CGS-S, CGI-I, CGAS, K-SADS.	Adolescents (12-17) with MDD Pbo: n=*155/126* Escit: n=*157/133* (*entered/ completed*) Mean age: 14.5	1° efficacy variable *Pbo:* -18.4± 1.1 *Cit:* -22.4 ± 1.1 **p=0.022** 2° efficacy variable: CGI-I: **p=0.008**
Study SCT-MD-15 25 US Centers	8 week, double blind, pbo controlled, flexible dose, escitaloprm 10-20 mg/d 1° efficacy variable: CDRS Δ from baseline to 8th week;	Children/adoles. (6-17) with MDD All Patients: Pbo: n=*133/115* Escital: n=*131/102* Subset of Adolescents: Pbo: n=81 Escital: n=79 Mean age: 12.3	**NEGATIVE** study results Pbo: -20.3±1.3 Escital: -20.9±1.3 **Greatest improvement in 12-17 y.o.**
LEXAPRO PEDIATRIC STUDIES—LONGER TERM PLACEBO CONTROLLED			
SCT-MD-32A 35 US Centers	fixed dose (10 or 20 mg/d) extension study of Study 32 Adolescent patients with MDD. Originally a 24 week open label study, several amendments later, it changed to a 16 week pbo controlled study .	Open label: n=*37/22* (escital: n=19; pbo: n=18) Double blind n=165	Results **uninterpretable** -Patients not re-randomized at beginning of study.

STUDY	DESIGN	POPULATION	RESULTS
	1° efficacy variable: Originally, time to premature discontinuation. Amended to CDRS Δ from baseline (visit 3 of Study 32) to 24th week (visit 9 of Study32A) 2° efficacy variable: Originally, Family Interaction (estimated with the McMaster Family Functioning Subscale) Amended to CGI-I score at Treatment Week 24.	(escital: n=*83/37*; pbo: n=*82/40*) Mean age =14.6	-design changed during study -high withdrawal rate
CITALOPRAM PEDIATRIC STUDIES—SHORT TERM PLACEBO CONTROLLED			
Study CIT-MD-18 (Originally submitted: 4/18/02) 21 US Centers	8 week double-blind, pbo-controlled, flexible dose citalopram (20-40 mg/d) study. 1° efficacy variable: CDRS Δ from baseline to 8th week; 2° efficacy variable: CGS-S, CGI-I, CGAS, K-SADS.	Children/adolescents (7-17) with MDD. Pbo group: n=38 (7-11yo) n= 47 (12-17) Cit group n=*45/36* (7-11) **n=***44/35* **(**12-17) Mean age = 12 years	1° efficacy variable *Pbo:* -16.5 ± 1.6 *Cit:* -21.7 ± 1.6 **p=0.038** **Greatest improvement in 12-17 y.o.**
Study 94404 Originally submitted: 4/18/02) 31 International sites	12 week double-blind, placebo controlled, flexible dose (10-40 mg/d) 1° efficacy variable: Kiddie-SADS-P Δ from baseline to 8th week;	Adolescents with MDD	**Negative study:** Improvement in both placebo and citalopram groups.

4.3 Review Strategy

There is only one study, Study 32, reviewed to evaluate efficacy data supporting the sponsor's escitalopram efficacy claim for the acute treatment of Major Depressive Disorder in the adolescent population. The other study, Study 18, (b) (4) was previously reviewed (Hearst: 9/12/02), and summary results are presented.

The safety data base for escitalopram in adolescents with MDD consists of two acute placebo controlled studies, Studies 32 and 15, in addition to the longer term extension Study 32A.

4.4 Data Quality and Integrity

According to internal FDA communications with DSI, there have been two inspection sites investigated. Both sites are determined to be acceptable to be considered for efficacy data. The formal DSI report is pending at the time of this review.

4.5 Compliance with Good Clinical Practices

According to internal FDA communications with DSI, the DSI report investigating two study sites find no violations that would compromise the efficacy findings of the pivotal study reviewed in this submission. The formal DSI report is pending at the time of this review.

4.6 Financial Disclosures

Executive Vice President and CMO of Forest Laboratories, Inc signed the Form 3454 testifying that, to his knowledge, there were no financial arrangements made with investigators that could affect the outcome of the studies as defined in 21 CFR 54.2 (a), and that no listed investigator (attached to the form) was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f) for the listing of investigators attached to each 3454.

The sponsor reports the following three investigators as having relevant financial disclosures:

1. (b) (4), investigator for Study (b) (4) This investigator owned 1,000 shares of Forest Laboratories stocks on November 18, 2002 with shares valued at $106.10 per share ($106,100);

2. (b) (4) sub-investigator, (b) (4) for (b) (4) received $37,515.00 to conduct an investigator initiated trial on the relationship between immune function and depression;

3. (b) (4), sub-investigator for (b) (4) received a total of $20,200.00, honoraria for speaking on behalf of Forest Laboratories Inc.

Although (b) (4) is the investigator for one of the larger sites for (b) (4), this is one of (b) (4) other sites in this placebo-controlled study. Because (b) (4) is double-blind placebo-

controlled, multi-centered with multiple investigators at each site, and that the sponsor analyzed each site's effect on the overall efficacy results, the sponsor has concluded that none of the financial disclosures above affected the study outcome results.

Studies 15 and 32A weren't used to support labeling claims; therefore, the financial disclosures listed for these studies need not be addressed for purposes of this review.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Escitalopram has a mean terminal half-life of about 27-32 hours with mainly hepatic biotransformation and renal clearance. In vitro studies using human liver microsomes indicate that CYP3A4 and CYP2C19 are the primary isozymes involved in the demethylation of escitalopram. The single and multiple dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10-30 mg/day. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in young healthy subjects was 2.2-2.5 times the plasma concentration observed after a single dose. Absorption of escitalopram is not affected by food.

5.2 Pharmacodynamics

Escitalopram is the S-enantiomer of racemic citalopram. 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 thought to be more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Escitalopram has no or very low affinity for serotonergic or other receptors including alpha- and beta-adrenergic, dopamine, histamine, muscarinic, and benzodiazepine receptors.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication for this supplement NDA is major depressive disorder (MDD) in the adolescent population. The current labeling for escitalopram includes the treatment of MDD in adults. DSM IV defines a major depressive episode as a relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes as 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.

To date, the DSM IV doesn't make a diagnostic distinction between adult and adolescent symptomatology for MDD.

6.1.1 Methods

For the purposes of determining the efficacy of escitalopram for the treatment of MDD in adolescents, the following two positive studies are considered the pivotal studies supporting the proposed indication:

1. **Study 32** – an 8 week, double-blind, placebo-controlled, **adolescent** (12-17), flexible dose (10-20 mg/d escitalopram) study:
   Entered: n=312;
   Completed: n=259: pbo: n=126 (81%)
   escitalopram: n=133 (85%)

2. **Study 18**- an 8 week double-blind, placebo-controlled, flexible dose (citalopram 20-40 mg/d) study in children (7-11) and adolescents (12-17):
   Children:
   Entered: n=83
   Completed: n=66: pbo: n=30 (78.9%)
   citalopram: n=36 (80%)
   Adolescents:
   Entered: n=91
   Completed: n=72: pbo: n=37 (78.7%)
   citalopram: n=35 (79.5%)

The other studies submitted in this escitalopram application can't be used to support efficacy in the proposed labeling. They include **Study 15** and **Study 32A**. Study 15 has negative results showing a statistically insignificant difference between placebo and study drug. The results of Study 32A are uninterpretable due to the following flaws in the study design: a) patients are not randomized at the beginning of this extension study (after completing the acute term Study 32), and b) the study design changes during the study from being open label to placebo controlled.

Because Study 15 and Study 32A can't be used to support labeling claims, they aren't reviewed for efficacy. However, they are included in the escitalopram safety data base for the adolescent population.

6.1.2 General Discussion of Endpoints

The primary efficacy variable of Study 32 is the Children's Depression Rating Scale-Revised (CDRS-R). The CDRS-R is a semi-structured, clinician-rated instrument designed for use with children and adolescents between the ages of 6-17 years. It contains 17 ordinally scaled items used to evaluate the presence and severity of symptoms commonly associated with depression in childhood. According to the protocol, the CDRS-R is administered separately to the patient and to the identified parent or caregiver.

The key secondary efficacy variable of Study 32 is the CGI-I. The CGI-I is a clinician-rated instrument used to rate the total improvement or worsening in a patient's mental illness, based on the Investigator's clinical opinion. The score ranges from 1 to 7, with 1 being very much improved and 7 being very much worse, relative to baseline. Scoring is independent of whether the Investigator considers any changes due to treatment with the study drug.

6.1.3 Study Design

6.1.3.1 Study **32**

Investigators/Location

This study is conducted in 40 study centers in the United States of which 38 centers randomized patients.

Objective(s)/Rationale

The objective of the study is to assess the safety and efficacy of escitalopram in the treatment of major depressive disorder in the adolescent population.

Population

Included in the study are physically healthy, adolescent outpatients (12-17 y.o.) with a diagnosis of a current major depressive episode for at least 12 weeks. Patients are required to have a CDRS-R score of ≥ 45, CGI score of ≥ 4, and IQ score ≥ 80 at the beginning of the double blind portion of the study. Female patients must have a negative serum pregnancy test, and, if sexually active, are required to use a reliable method of birth control.

Excluded from the study are patients who have any concomitant psychiatric diagnosis, psychotic symptoms, are a suicide risk, or have a history of the following: substance abuse/dependence with in the past year, positive urine drug screen, first degree relative with bipolar disorder, seizures.

No antidepressant or anxiolytic medications are allowed for 2 weeks prior to the study. Fluoxetine must be terminated 4 week prior to the study, and patients may not be treated with any neuroleptic or stimulant for 6 months prior to the study.

Neither psychotherapy nor behavioral therapy are allowed to be started within 3 months prior to the study, and no changes in talking therapy may be done during the study.

Design

This is a double blind, randomized, placebo-controlled, flexible dose (10-20 mg escitalopram), 8 week study. The study is preceded by a 2 week screening period, which includes a single-blind placebo lead-in during the second week. The study ends with a one week double blind tapering schedule.

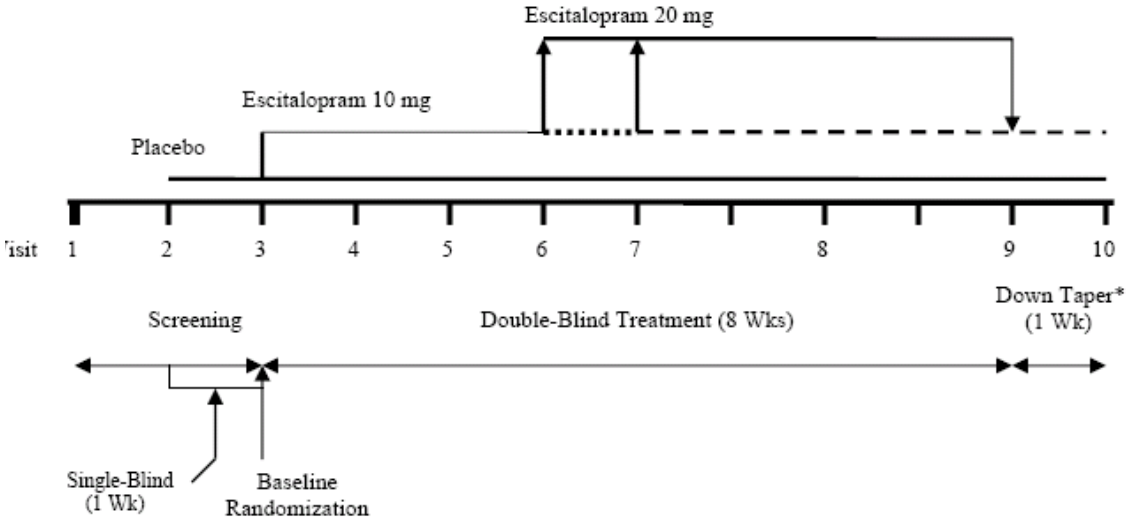
It is unclear if a psychiatric interview was conducted to make the diagnosis of MDD. In the protocol, it states that psychiatric history was collected, and that two different clinicians must be in agreement regarding the findings from two structured interview questionnaires (the K-SADS-PL and the KBIT). However, it appears that the diagnosis was not made during a clinical interview.

After the one week placebo lead in, patients are then randomized to either escitalopram or placebo group. All patients in the escitalopram group are given 10 mg escitalopram for the first 3 weeks, and then at Week 3 or 4, and upon investigator evaluation of each patient for dose limited adverse events, the dose of escitalopram could be increased to 20 mg daily. The dose given at Week 4 (i.e. 10 or 20 mg) is continued for the remainder of the study; if adverse events occur, patients may return to the 10 mg dose.

An optional "down taper" week is available for patients who chose to not enter the extension study or who terminate the study prematurely. During this period, patients are given either 10 mg escitalopram or placebo, depending on their randomized assignment group at the beginning of the study.

All medication are administered as one tablet daily at evening, but can be switched to morning time.

Figure 6.1.3.1a Sponsor's schematic of the study design for Study 32



* Optional for patients not continuing into the extension study

Analysis Plan

The primary efficacy variable is the change from baseline to week 8 of the CDRS-R total score. The primary analysis is performed using the LOCF approach. Comparison between escitalopram and placebo is performed by a two way ANCOVA model with treatment group and study center as factors and baseline CDRS-R as a covariate. The secondary efficacy variable is the CGI-I at Week 8.

A history and physical is conducted at screening. At screening and termination, the following evaluations are done: routine lab, serum pregnancy tests, thyroid function test, UDS, and ECG. Vitals are assessed weekly throughout the study. Please see Appendix 1 for the sponsor's Schedule of Events.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 584 patients screened for the study, 316 patients are randomized into double-blind treatment. Reasons given for ineligibility include the following: entry criteria not met (n=201), adverse event (n=1), protocol violation (n=5), lost to follow-up (n=17), withdrew consent (n=37), and "other" (n=7). Of the 316 patients in the intent-to-treat population, there are 4 patients who withdrew before the first dose, and aren't considered part of the efficacy or safety population. Therefore, 312 patients are in the efficacy/safety population; however, there are 311 patients in the ITT with at least one post-baseline CDRS-R assessment. Of the 157 patients

randomized to placebo, 133 (85%) completed the study; of the 155 patients randomized to escitalopram treatment, 126 (80%) completed the study. Table 6.1.3.1b (below) summarizes the reasons for early withdrawal.

As can be seen from Table 6.1.3.1b, discontinuations due to adverse events are more prevalent in the escitalopram group compared to the placebo group. Otherwise, there are no statistically significant difference between the escitalopram and the placebo groups with regard to reasons for early withdrawal.

Table 6.1.3.1b Reasons for early withdrawal for Study 32
(sponsor table from Study 32 study report)

	Placebo (N = 157) n (%)	*Escitalopram (N = 155) n (%)*	*Total (N = 312) n (%)*
Prematurely discontinued	24 (15.3)	29 (18.7)	53 (17.0)
Reason for discontinuation			
Adverse event	1 (0.6)	4 (2.6)	5 (1.6)
Insufficient therapeutic response	5 (3.2)	5 (3.2)	10 (3.2)
Protocol violation, including lack of compliance	0	3 (1.9)	3 (1.0)
Withdrawal of consent	9 (5.7)	8 (5.2)	17 (5.4)
Lost to follow-up	6 (3.8)	8 (5.2)	14 (4.5)
Other	3 (1.9)[a]	1 (0.6)[b]	4 (1.3)

Demographics /Group Comparability

The majority of the patients in this study are Caucasian females with a mean age of 14.6 years old (range of 13 to16). The population consists of 184 females (59%) and 128 (41%) males of which there are 236 (75.6%) Caucasians, 54 (17.3%) African-Americans, 3 (1 %) Asian, and 19 (6.1%) "other." The sponsor reports that there are no statistically significant differences between the treatment groups with respect to demographics.

Concomitant Medications

Concomitant medications used most frequently include the sponsor's general categories of "analgesics" and "anti-inflammatory and anti-rheumatic products" (the sponsor does not provide the specific medications within these categories); both these categories appear to be used comparably in both the placebo and escitalopram group. It is noted that "drugs for acid related disorder" and "sex hormones and modulator of the genital systems" are used by more patients in the escitalopram group than in the placebo group; however, this trend is also observed at baseline (see 6.1.3.1c below). It is unclear what the sponsor is referring to as "psycholeptics" which were used by 5.2 % (n=8) of escitalopram patients and 4.5 % (n= 7) of placebo patients.

Table 6.1.3.1c Notable differences in concomitant medications:

MEDICATION GROUP	BASELINE		DURING STUDY	
	Escitalopram (n=155)	Placebo (n=157)	Escitalopram (n=155)	Placebo (n=157)
Drugs for acid related disorders	10 (6.5%)	2 (1.3)	14 (9.0)	7 (4.5)
Sex hormones and modulators of the genital system	15 (9.7)	8 (5.1)	15 (9.7)	9 (5.7)

Efficacy Results

The sponsor reports a statistically significant difference (p-0.022) comparing the escitalopram and placebo groups in change from baseline to Week 8 of the primary efficacy instrument, the CDRS-R total score. The sponsor also reports a statistically significant difference comparing the two treatment groups in the change from baseline to Week 8 in the CGI-I score, the key secondary variable (p=0.008). These findings are verified and supported by the FDA statistical reviewer, Dr. George Kordzakhia (1/28/09). Dr. Kordzakhia also confirms the sponsor's analysis for the primary efficacy variable using the mixed-effects model for repeated measures (MMRM); his findings again support the primary analysis results.

Of the 154 intent-to-treat patients treated by escitalopram, 54 had 10mg on their last visit, and 100 patients received 20mg on their last visit.

In a subgroup analysis, Dr. Kordzakhia notes that patients categorized as African American did not demonstrate an improvement in the primary efficacy variable with escitalopram treatment (see Table 6.1.3.1d).

Table 6.1.3.1d Subgroup Analysis: CDRS-RS Total score mean change from baseline with missing values imputed by LOCF method (adapted from Statistical Review and Evaluation by George Kordzakhia, Ph.D., draft: 1/28/09)

Subgroup	**Placebo**		**Escitalopram**		**Treatment Difference: Escitalopram - Placebo**	
	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean (SE)	95% CI
Gender						
Male	65	-18.75 (1.70)	62	-21.84 (1.74)	-3.09 (2.45)	(-7.93, 1.75)
Female	92	-18.81 (1.36)	92	-22.25 (1.36)	-3.44 (1.93)	(-7.24, 0.37)
Race						
White	123	-17.90 (1.19)	112	-22.73 (1.25)	-4.83 ((1.72)	(-8.23, -1.43)
African American	24	-24.74 (2.39)	30	-18.38 (2.13)	6.36 (3.26)	(-0.17, 12.90)
Other	10	-18.22 (5.29)	12	-22.90 (4.83)	-4.67 (7.17)	(-19.67, 10.32)

Conclusions for Study 32

The statistical results of this study support the sponsor's claim that escitalopram is effective in the treatment of major depressive disorder (as defined in this protocol) in the adolescent population.

One possible flaw in this study is that it is unclear if a psychiatric interview was conducted to make the diagnosis of MDD. In the protocol, it states that psychiatric history was collected, and that two different clinicians must be in agreement regarding the findings from two structured interview questionnaires (the K-SADS-PL and the KBIT). However, it appears that the diagnosis was not made by a clinical interview with a trained clinician.

6.1.3.2 **Study 32A**

Study 32A is presented by the sponsor to support the labeling for a longer term use of escitalopram to treat MDD in the adolescent population.

Because of major flaws in the design of Study 32A, it can't be used to support efficacy labeling claims. Study 32A was originally designed as a 24 week open-label, flexible-dose, extension study. After the study began and patient data was collected, the protocol was amended several times to evolve into a 16 week, double blind, placebo controlled, extension study.

Most importantly, the study design doesn't re-randomized patient assignment at the beginning of Study 32A after completing Study 32. As Dr. Chen points out in her SAP review (10/10/07), when the data of the acute phase (Study 32) is combined with the long-term phase (Study 32A), coupled with a high drop out rate, the maintenance effect would be confounded with the acute effect. Study 32A has an almost 75% drop out rate for both treatment groups (Kordzakhia, 1/28/09).

Because of the high drop out rate, and that patients are not re-randomized prior to beginning Study 32A, the data for this study is considered uninterpretable.

6.1.3.3 **Study 15**

Study 15 is a double-blind, placebo-controlled, flexible dose (10-20 mg/d **escitalopram**), 8 week study in children and adolescents (aged 6-17) diagnosed with MDD. There are 263 participants in this study (129 on escitalopram), with a mean age of 12.3 years. This study doesn't demonstrate a statistical significance (p=0.084) when comparing the treatment groups' change from baseline to eight weeks of the primary efficacy variable (CDRS-R). Therefore, this is considered a negative study and isn't reviewed for efficacy. Study 15 is included in the safety

data base. It's noted that the sponsor's post-hoc analysis by age revealed that the adolescent (12-17) group demonstrates a greater improvement in the primary efficacy variable than patients under 12 y.o.

6.1.3.4 **Study 18**

In April, 2002, Study 18 (b) (4) **citalopram**, the racemic mixture which includes escitalopram. Dr. Earl Hearst, FDA clinical reviewer, reviewed this positive study, in addition to the negative Study 94404 (9/12/02). (b) (4) Later it was determined that Study 18 could used as one of the two positive studies required to support pediatric labeling for escitalopram (an isomer of citalopram) in the treatment of MDD (DPP letter of 11/16/04).

Study 18 is an 8 week, randomized, double-blind, placebo-controlled, flexible dose citalopram (20-40 mg/d) study conducted in 160 pediatric patients (aged 7-17) diagnosed with MDD. The treatment groups are stratified for age group (children: 7-11 and adolescents: 12-17). The primary efficacy variable is the change from baseline to 8 weeks comparing the placebo and citalopram groups on the Children's Depression Rating Scale-Revised (CDRS-R). As discussed in Dr. Hearst's review (9/12/02), the placebo group included 38 patients aged 7-11 y.o. and 47 patients 12-17 y.o. The mean age in both treatment groups is 12 y.o. with the majority of patient being female (53% for citalopram and 54 % for placebo) and Caucasian (81% and 73%, respectively). The following is a further breakdown of the patient population by age:

Children (7-11):
Entered: n=83
Completed: n=66: pbo: n=30 (78.9%)
citalopram: n=36 (80%)

Adolescents (12-17):
Entered: n=91
Completed: n=72: pbo: n=37 (78.7%)
citalopram: n=35 (79.5%)

The study is positive for the primary efficacy variable of change from baseline of the CDRS-R total Score (p=0.038). As can be seen from Table 6.1.3.4, there is a greater improvement for the adolescent group than the children group when comparing the differences to placebo. As Dr. Laughren notes in his memo of 9/16/02, "…it appears that the positive results for this trial are coming largely from the adolescent subgroup."

Table 6.1.3.4 Summary of primary efficacy variable for Study 18 by age subgroups
(extracted from Memorandum by Laughren: 9/16/02).

Efficacy Results (Children) on CDRS-R Total Score for Study CIT-MD-18 (LOCF)

	Mean Baseline CDRS-R	Mean O baseline CDRS-R
Citalopram	**60.0**	**-20.9**
Placebo	**56.8**	**-17.1**

Efficacy Results (Adolescents) on CDRS-R Total Score for Study CIT-MD-18 (LOCF)

	Mean Baseline CDRS-R	Mean O baseline CDRS-R
Citalopram	**57.5**	**-22.6**
Placebo	**58.6**	**-15.4**

6.1.4 Efficacy Conclusions

Study 32 has positive results supporting the labeling claim that escitalopram is an effective acute treatment for adolescents diagnosed with major depressive disorder (MDD). It is noted that the other acute escitalopram study (Study 15) has negative results.

There are several medications effective in treating adults with MDD that haven't been able to prove effective in the pediatric population in the required placebo-controlled design. Because of the paucity of positive pediatric studies in MDD, DPP requires two positive studies in the pediatric population to support a labeling claim for MDD in children and adolescents.

It is agreed between the sponsor and FDA that the one positive citalopram, placebo-controlled, study in the pediatric population diagnosed with MDD can be used to support labeling claims for escitalopram. The rationale behind this agreement rests in the concept that escitalopram in the S-isomer of the racemic compound citalopram.

Study 32A, submitted by the sponsor to support a maintenance claim for adolescents, has uninterpretable results due to design flaws. However, a long term claim in the adolescent population can be extrapolated from adult data, because the following conditions have been met: 1) short term pediatric efficacy is demonstrated in two acute placebo controlled studies, and 2) efficacy has been established for adult longer term treatment.

In conclusion, given the positive results of the escitalopram Study 32, and the citalopram Study 18, the sponsor has fulfilled FDA requirements to support the claim that escitalopram is effective in the treatment of acute treatment of MDD in the adolescent population. Longer term maintenance claim in for the adolescent population is supported by extrapolation from adult data.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review focuses on the sponsor's escitalopram (Lexapro®) safety data base for pediatric patients diagnosed with major depressive disorder (MDD). In their current application, the sponsor includes data from the racemic compound, citalopram (Celexa®). The safety data base from the pediatric citalopram placebo-controlled and pharmacokinetic studies were previously reviewed in depth by FDA (see Hearst: 9/12/02) and has a safety profile consistent with the label for the adult MDD indication. This review will include only significant findings in the pediatric citalopram longer term open label extension Studies 18 and 19, and make mention of any significant findings in the pediatric citalopram studies previously reviewed.

The cut-off date for this safety data base is December 31, 2007. All the escitalopram and citalopram studies considered for this pediatric claim have completion dates prior to this submission. The safety update covers the period of January to May, 2008, and includes pediatric data from post-marketing spontaneous reports (see Section 7.2.9 below).

7.1.1 Deaths

There are no deaths reported in this pediatric safety data base.

7.1.2 Other Serious Adverse Events (SAE)

Table 7.1.2a, below, summarizes the incidence of serious adverse events in the pediatric MDD population exposed to escitalopram (Celexa®). As can be seen from this table, there doesn't appear to be any significant findings when comparing escitalopram and placebo groups.

In the citalopram safety data base, the most common SAE for the citalopram placebo controlled study 944404 was suicide attempt (citolopram: n= 13 pbo: n=4). In addition to these cases, the sponsor reports one placebo and one citalopram patient with suicidal ideation or tendency. In the citalopram extended long term study 20, there is one ECG abnormality noted (no details provided in ISS).

Please see Table 7.1.2b, below, for the sponsor's summary table of SAEs in the escitalopram safety data base. Narratives of these cases reveal 4 escitalopram SAEs attributed to suicidal gestures or attempts, and 1 patient hospitalized for increased irritability; 5 placebo patients have SAE of suicidal gestures/attempts and 1 SAE of increased depression

Table 7.1.2a Incidence of Adverse Events in the pediatric escitalopram clinical studies
(extracted from the Sponsor's ISS)

Age Range, y; Event	*No. (%) of Patients*				
	Short-term Studies		*All Studies*		
	SCT-MD-15 and SCT-MD-32		*SCT-MD-15, SCT-MD-32, and SCT-MD-32A*		
	Placebo	**Escitalopram**	**Placebo**	**Escitalopram**	**Open-Label Escitalopram**
Adolescents (12-17)					
N	238	234	238	234	37
Death	0	0	0	0	0
SAE	5 (2.1)	4 (1.7)	7 (2.9)	6 (2.6)	2 (5.4)
AE discontinuation	3 (1.3)	6 (2.6)	3 (1.3)	10 (4.3)	2 (5.4)
TEAE	174 (73.1)	177 (75.6)	181 (76.1)	184 (78.6)	32 (86.5)
Children (6-11)—Study SCT-MD-15 only					
N	52	52	52	52	—
Death	0	0	0	0	—
SAE	0	2 (3.8)	0	2 (3.8)	—
AE discontinuation	0	0	0	0	—
TEAE	34 (65.4)	34 (65.4)	34 (65.4)	34 (65.4)	—
All ages (6-17)					
N	290	286	290	286	37
Death	0	0	0	0	0
SAE	5 (1.7)	6 (2.1)	7 (2.4)	8 (2.8)	2 (5.4)
AE discontinuation	3 (1.0)	6 (2.1)	3 (1.0)	10 (3.5)	2 (5.4)
TEAE	208 (71.7)	211 (73.8)	215 (74.1)	218 (76.2)	32 (86.5)

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Cross-reference: After-Text Tables 5.1.1, 5.1.2, 5.1.3, 5.4.1A, 5.4.1B, 5.4.3A, and 5.4.3B; Study SCT-MD-32/32A, Tables 14.5.1.1A and 14.5.1.1C.

Table 7.1.2b Adolescent patients with serious adverse events (SAEs) in the escitalopram safety data base (extracted from Sponsor's ISS table 5.1.4.1-1)

Study	*Patient ID*	*Age, y/ Sex*	*Days on Study Drug*[a]	*SAE Start Day*[b]	*Preferred Term*	*Investigator Term*
Before first dose of study drug (not randomized)						
SCT-MD-32	0243207	13/F	—	—	Suicidal tendency	Suicidal ideation
				—	Depression aggravated	Severity of depressive symptoms
Placebo						
SCT-MD-15	0071506	13/M	56	72	Allergic reaction	Allergic response to a virus
SCT-MD-15	0081514	17/M	52	51	Manic reaction	Manic episode[c,d]
SCT-MD-15	0261508	14/M	7	22	Depression	Hospitalization for depression
SCT-MD-32	0323202	13/F	45	55	Suicidal tendency	Intensified suicidal ideation[d,e]
SCT-MD-32	0353212	14/F	5	5	Depression aggravated	Worsening depression[c,d]
SCT-MD-32A	0343202	17/F	228	149	Suicidal tendency	Threatening to cut herself
SCT-MD-32A	0383225	16/M	174	197	Suicide attempt	Suicide attempt[f]
Escitalopram						
SCT-MD-32	0243210	17/F	57	53	Inflicted injury	Sexual assault upon patient
SCT-MD-32	0283210	16/M	33	44	Suicidal tendency	Intensified suicidal ideation requiring psychiatric hospitalization
SCT-MD-32	0443209	14/M	10	14	Irritability	Exacerbation of increased irritability[d]
SCT-MD-32	0453202	16/F	49	50	Inflicted injury	Self-injurious behavior with no suicidal intent[c]
SCT-MD-32A	0213204	12/M	104	99	Failure to thrive	Failure to thrive[c]
SCT-MD-32A	0373212	14/M	75	95	Suicidal tendency	Self-harm gesture
Open-label escitalopram						
SCT-MD-32A	0033206	15/F	80	80	Non-accidental overdose	Intentional overdose of study medication[c]
SCT-MD-32A	0103201	12/M	153	130	Pleuritis	Viral pleurodynia

7.1.3 Dropouts and Other Significant Adverse Events

The incidence of premature withdrawal is significantly greater in the escitalopram groups compared to the placebo group (4.3% vs. 1.3%). The most common AE associated with withdrawal in the escitalopram group is insomnia; self inflicted injury, fatigue and restlessness are more prevalent in the escitalopram group compared to placebo. Please refer to Table 7.1.3 below for further details. Narratives of early withdrawals describe symptomatology already described in current escitalopram labeling.

Table 7.1.3 Incidence of patients with common AE (n ≥ 2 patients) leading to premature discontinuation in the escitalopram safety data base. (extracted from sponsor's ISS Table 5.1.5-1)

Preferred Term	*No. (%) of Patients*				
	Short-term Studies		*All Studies*		
	SCT-MD-15 and SCT-MD-32		**SCT-MD-15, SCT-MD-32, and SCT-MD-32A**		
	Placebo (N = 238)	*ESC (N = 234)*	*Placebo (N = 238)*	*ESC (N = 234)*	*Open-Label ESC (N = 37)*
Patients with ≥ 1 AE leading to premature discontinuation	3 (1.3)	6 (2.6)	3 (1.3)	10 (4.3)	2 (5.4)
Insomnia	0	2 (0.9)	0	3 (1.3)	0
Fatigue	0	1 (0.4)	0	2 (0.9)	0
Inflicted injury	0	1 (0.4)	0	2 (0.9)	0
Restlessness aggravated	0	2 (0.9)	0	2 (0.9)	0

7.1.4 Other Search Strategies

There were no other search strategies utilized in this review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

It is unclear from the protocols if adverse events were specifically solicited or if adverse events were noted only when a patient made specific complaints. The protocols merely state that patients are "queried" regarding AEs.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor groups treatment-emergent adverse events by occurrence. It is unclear from this submission what classification system/dictionary is used to classify events.

7.1.5.3 Incidence of common adverse events

Common AEs occurring with greater frequency in the escitalopram group compared to placebo in acute studies include the following: **headache,** abdominal pain, nausea, and insomnia; headache was identified as the most common treatment emergent AE in the adolescent escitalopram data base. In the longer term escitalopram study, diarrhea and urinary tract infections (UTI) are also considered common AEs (note: UTI is reported in ≥ 5 % of escitalopram patients with an incidence of ≥ 2 times observed in placebo patients).

Below, Tables 7.1.5.3a (acute escitalopram studies) and 7.1.5.3b (longer term escitalopram study), summarize the common AEs in the escitalopram adolescent safety data base.

Table 7.1.5.3a Common treatment-emergent AE ≥ 5% in short-term escitalopram studies for adolescent safety data base only. (extracted from sponsor's ISS Table 5.1.2.1.1-1)

Preferred Term	*Placebo, n (%) (N = 238)*	*Escitalopram, n (%) (N = 234)*
Patients with ≥ 1 TEAE	174 (73.1)	177 (75.6)
Headache	56 (23.5)	57 (24.4)
Abdominal pain	14 (5.9)	23 (9.8)
Nausea	17 (7.1)	22 (9.4)
Insomnia	12 (5.0)	21 (9.0)
Menstrual cramps[a]	21 (15.1)	12 (8.9)
Pharyngitis	18 (7.6)	19 (8.1)
Inflicted injury	25 (10.5)	18 (7.7)
Rhinitis	16 (6.7)	16 (6.8)
Fatigue	15 (6.3)	14 (6.0)
Upper respiratory tract infection	18 (7.6)	13 (5.6)
Vomiting	12 (5.0)	13 (5.6)
Influenza-like symptoms	10 (4.2)	12 (5.1)

Studies SCT-MD-32 and SCT-MD-15.
a Female population only: placebo, N = 139; escitalopram, N = 135.
TEAE = treatment-emergent adverse event.

Table 7.1.5.3b Common treatment-emergent AE ≥ 5% in longer term adolescent escitalopram Study 32/32A (extracted from sponsor's ISS Table 5.1.2.1.4-1) ***

Preferred Term	*Placebo, n (%) (N = 157)*	*Escitalopram, n (%) (N = 155)*
Patients with ≥ 1 TEAE	125 (79.6)	128 (82.6)
Headache	44 (28.0)	44 (28.4)
Inflicted injury	32 (20.4)	24 (15.5)
Menstrual cramps[a]	14 (15.2)	12 (13.0)
Nausea	15 (9.6)	18 (11.6)
Insomnia	11 (7.0)	17 (11.0)
Pharyngitis	20 (12.7)	17 (11.0)
Rhinitis	23 (14.6)	15 (9.7)
Abdominal pain	15 (9.6)	14 (9.0)
Upper respiratory tract infection	22 (14.0)	14 (9.0)
Vomiting	9 (5.7)	14 (9.0)
Fatigue	15 (9.6)	13 (8.4)
Influenza-like symptoms	9 (5.7)	13 (8.4)
Diarrhea	6 (3.8)	8 (5.2)
Urinary tract infection	2 (1.3)	8 (5.2)
Coughing	13 (8.3)	6 (3.9)
Appetite decreased	8 (5.1)	4 (2.6)

***REVIEWER'S NOTE: "N" in the 1st line heading under "Placebo" and "Escitalopram" is inflated as this is a pooled table including patients in Study 32. The true "N" for the longer term Study 32A is the following: *Escitalopram:* n=83 entering /37 completing; *Placebo* : n=82 entering/40 completing)**

7.1.5.4 Common adverse event tables

The identified common AEs are consistent with the current adult labeling. Although the sponsor does not present a new common adverse events table in their proposed labeling for this supplement, it is helpful to have specific information regarding the adolescent population in at least the foot notes of the common AE table in labeling.

7.1.6 Suicidality

Please refer to Table 7.1.6a for the incidence treatment-emergent AE potentially associated with suicidal behavior in the escitalopram adolescent safety data base. For self-inflicted injury, it appears that there was a greater treatment-emergent incidence in the escitalopram safety data base compared to the placebo. Table 7.1.6 b summarizes the suicidal gestures/attempts described in the narratives in this safety data base.

Table 7.1.6a Incidence of patients with treatment-emergent AE potentially associated with suicidal behavior in the escitalopram adolescent safety data base.
(Table extracted from ISS Table 5.1.6.1.1.1-1)

Preferred Term	*No. (%) of Patients*				
	Short-term Studies		*All Studies*		
	SCT-MD-15 and SCT-MD-32		**SCT-MD-15, SCT-MD-32, and SCT-MD-32A**		
	***Placebo* (N = 238)**	***ESC* (N = 234)**	***Placebo* (N = 238)**	***ESC* (N = 234)**	***Open-Label ESC* (N = 37)**
Suicide attempt[a]	0	0	1 (0.4)[b]	0	0
Suicidal tendency[c]	3 (1.3)	1 (0.4)	4 (1.7)	2 (0.9)	1 (2.7)
Non-accidental overdose	2 (0.8)	0	2 (0.8)	0	1 (2.7)
Accidental overdose	0	0	0	0	1 (2.7)
Inflicted injury[d]	25 (10.5)	18 (7.7)	36 (15.1)	28 (12.0)	7 (18.9)
Self-inflicted injury[e,f]	4 (1.7)	7 (3.0)	7 (2.9)	11 (4.7)	1 (2.7)

c Suicidal tendency was also reported in Study SCT-MD-32 for Patient 0243207, who failed screening and did not receive study drug.

d Inflicted injury (sore shoulder due to fall) was also reported in Study SCT-MD-32 for Patient 0073212, who failed screening and did not receive study drug.

e Treatment-emergent adverse events coded to inflicted injury that were specifically indicated by the Investigator in Studies SCT-MD-32 and SCT-MD-32A as suggestive of self-harm or that were indicated as self-inflicted in the Investigator's description of the events. Two escitalopram patients (0033213 and 0383211) had self-injurious events in both Studies SCT-MD-32 and SCT-MD-32A.

f One additional patient (0033214) in Study SCT-MD-32 reported inflicted injury that was considered by the Investigator to be self-injurious, non-suicidal. The event occurred before the start of study medication; the patient subsequently received double-blind escitalopram.

Table 7.1.6b Patient summaries of treatment-emergent self harm/self-inflicted injuries in escitalopram adolescent data base. (extracted from sponsor's ISS Table 5.1.6.1.1.1-2)

Study	*Patient ID*	*Age, y/ Sex*	*Days on Study Drug*[a]	*TEAE Start Day*[b]	*Investigator Term*
Placebo					
SCT-MD-32	0103205	14/F	45	28	Superficial cutting
SCT-MD-32	0193205	14/F	134	4	Superficial scratches left arm[c]
SCT-MD-32	0323202	13/F	45	58	Self-injurious cuts on left arm and thighs[c,d]
SCT-MD-32	0443210	14/F	56	5	Self-mutilation
				39	Contusion left lower leg, accident, no suicidal ideation[i]
SCT-MD-32A	0033211	15/F	229	109	Superficial abrasion left arm
				230	Injury right hand with mild aching pain, diagnosed broken
SCT-MD-32A	0343202	17/F	228	147	Superficial cutting[e]
SCT-MD-32A	0383225	16/M	174	103	Superficial cutting to left thigh[f]
				144	Self-inflicted cutting to left thigh[f]
Escitalopram					
SCT-MD-15	0331509	16/M	14	10	Self-inflicted laceration to right wrist
SCT-MD-32	0193219	13/F	96	29	Contusion (left elbow; after accidentally fall)[i]
				54	Non-suicidal self-injurious behavior[c]
SCT-MD-32	0343201	12/F	106	38	Superficial cutting

Study	*Patient ID*	*Age, y/ Sex*	*Days on Study Drug*[a]	*TEAE Start Day*[b]	*Investigator Term*
SCT-MD-32	0453202	16/F	49	50	Self-injurious behavior with no suicidal intent[g,h]
SCT-MD-32	0493209	12/F	131	56	Superficial right wrist cuts
SCT-MD-32A	0203206	16/F	83	74	Abrasions on both forearms[i]
				79	Laceration left inguinal region[c]
SCT-MD-32A	0333206	16/F	141	135	Laceration to left wrist
SCT-MD-32A	0353214	16/F	73	66	Superficial cutting on arm[c,g]
SCT-MD-32A	0383202	13/F	227	86	Abrasions to left foot, arm, elbow and left lower quadrant of abdomen[i]
				173	Self-inflicted cutting to right lower leg
SCT-MD-32/32A	0033213	16/M	224	33	Injured fist after hitting the wall following an argument with Dad[c]
				143	Possible concussion, no LOC[i]
				156	Contusion left hand[i]
SCT-MD-32/32A	0383211	16/F	102	1	Self-inflicted scratches on forearm
				35	Cutting—shallow lacerations
				66	Poking finger tips with pin
Open-label escitalopram					
SCT-MD-32A	0113201	14/F	174	10	Cut on self

The sponsor also uses the following two instruments to assess improvement in suicidality: 1) the Modified Columbia-Suicide Severity Rating Scale (**MC-SSRS**) and, 2) the Suicidal Ideation Questionnaire-Junior High School Version (**SIQ-JR**).

For Study 32 (acute, placebo-controlled, adolescent escitalopram positive study), it appears that numerically, the placebo group actually demonstrates a greater improvement in the **SIQ-JR** than the escitalopram group. The mean changes from baseline of the SIQ-JR scores (mean ± SD) are –5.8 ± 12.8 for placebo patients and –3.0 ± 11.7 for escitalopram patients. As the sponsor points out, it is difficult to make conclusions based on these results as the study is not powered to detect this difference.

MC-SSRS scores from Studies 32 and 32A (the acute and longer term, placebo-controlled, adolescent escitalopram studies) demonstrate an increase from baseline in MC-SSRS scores for all treatment groups, suggesting a more severe level of suicidality (see Table 7.1.6c). The

implication of these scores is that suicidal ideation has a greater incidence in escitalopram patients compared to the placebo group in the longer term data base of Study 32A, and that escitalopram patients tended to have more severe levels of suicidal ideation than placebo patients.

Table 7.1.6c Number and percentage of adolescent patient with an increase from baseline in the MC-SSRS Scores (extracted from sponsor ISS Table 5.1.6.1.1.3-1)

	Study SCT-MD-32		*Studies SCT-MD-32 and SCT-MD-32A*	
	Placebo, n (%) (N = 128)	*Escitalopram, n (%) (N = 131)*	*Placebo, n (%) (N = 128)*	*Escitalopram, n (%) (N = 131)*
Any suicidal behavior and/or ideation	13 (10.2)	12 (9.2)	14 (10.9)	19 (14.5)
Suicidal behavior	3 (2.3)	2 (1.5)	3 (2.3)	4 (3.1)
Suicidal ideation	12 (9.4)	12 (9.2)	13 (10.2)	19 (14.5)
Modal (most common)	10 (7.8)	6 (4.6)	11 (8.6)	9 (6.9)
Most severe	10 (7.8)	12 (9.2)	11 (8.6)	19 (14.5)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests are performed at baseline and Week 8 (or early withdrawal) for the acute study and again at week 24 for the longer term study.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This review discusses the two short term pediatric MDD placebo-controlled escitalopram studies, Studies 15 and 32, and the longer term escitalopram study, Study 32A.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

When comparing the mean change from baseline of all laboratory values in the escitalopram adolescent MDD safety data base, there is no apparent significant difference between the escitalopram and placebo groups. It is noted that the mean increase for AST is higher in the

escitalopram group than in the placebo group. Please see Table 7.1.7.3.1, below, for a summary of mean change from baseline to endpoint of select clinical laboratory parameters.

Table 7.1.7.3.1 Mean change from baseline to end point in select clinical laboratory parameters in short term adolescent MDD escitalopram clinical studies. (extracted from ISS Table 6.3.1-2)

Parameter (Units)	*Placebo*			*Escitalopram*		
	n	*Baseline, Mean ± SD*	*Change, Mean ± SD*	*n*	*Baseline, Mean ± SD*	*Change, Mean ± SD*
Hematology						
Eosinophils (%)	215	2.4 ± 1.9	–0.0 ± 1.4	209	2.5 ± 2.0	–0.1 ± 1.5
Hemoglobin (mmol/L)	216	8.7 ± 0.7	–0.1 ± 0.4	209	8.6 ± 0.8	–0.2 ± 0.4
Chemistry						
ALT (U/L)	220	17.8 ± 8.9	–0.3 ± 8.7	212	18.5 ± 9.9	0.0 ± 7.6
AST (U/L)	220	20.7 ± 5.5	–0.1 ± 8.6	212	21.4 ± 6.4	0.9 ± 7.0
Bilirubin, total (µmol/L)	220	7.6 ± 5.5	–0.5 ± 3.5	212	7.3 ± 5.7	–0.1 ± 3.4
Potassium (mmol/L)	220	4.3 ± 0.4	–0.0 ± 0.5	213	4.3 ± 0.4	–0.1 ± 0.4

Note: Studies SCT-MD-32 and SCT-MD-15.
End point = last available postbaseline assessment.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; n = number of patients with a screening assessment and at least one postbaseline assessment.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

There are no early withdrawals due to laboratory value abnormalities (however, note that laboratory values are generally not obtained until completion of the study). Table 7.1.7.3.2 lists the incidence of PCS (potentially clinically significant) laboratory values in each treatment group in the adolescent escitalopram MDD safety data base.

Please see Appendix Table 2 for further details of patients presenting with potentially clinically significant post-baseline values in LFT.

Table 7.1.7.3.2 Incidence of patients with potentially clinically significant post-baseline laboratory parameters in escitalopram adolescent MDD patient population
(extracted from ISS Table 6.3.1-1)

Parameter	*PCS Criteria (Units)*	*Short-Term Studies*		*All Studies*		
		SCT-MD-15 and SCT-MD-32		*SCT-MD-15, SCT-MD-32, and SCT-MD-32A*		
		Placebo, n/N (%)	**ESC, n/N (%)**	**Placebo, n/N (%)**	**ESC, n/N (%)**	**Open-Label ESC, n**
Hematology						
Eosinophils	≥ 10%	2/214 (0.9)	1/207 (0.5)	5/215 (2.3)	1/208 (0.5)	1
Hemoglobin	≤ 0.9 × LLN (mmol/L)	0/216	1/209 (0.5)	0/217	1/210 (0.5)	0
Chemistry						
ALT	≥ 3 × ULN (U/L)	1/220 (0.5)	0/212	1/221 (0.5)	0/212	0
AST	≥ 3 × ULN (U/L)	1/220 (0.5)	1/212 (0.5)	1/221 (0.5)	1/212 (0.5)	1
Bilirubin, total	≥ 34.2 µmol/L	0/219	1/211 (0.5)	1/220 (0.5)	1/211 (0.5)	0
Potassium	≥ 5.5 mmol/L	1/218 (0.5)	0/209	2/219 (0.9)	0/209	0
Urinalysis						
Glucose	≥ 2+	3/216 (1.4)	0/210	3/217 (1.4)	0/210	0
Protein	≥ 2+	4/214 (1.9)	4/209 (1.9)	5/215 (2.3)	4/209 (1.9)	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ESC = escitalopram; LLN = lower limit of normal; n = number of patients with a non-PCS baseline value who met criterion at least once during double-blind treatment; N = number of patients with a non-PCS baseline assessment and at least one postbaseline assessment; PCS = potentially clinically significant; ULN = upper limit of normal.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the short term studies (15 and 32), vital signs monitored weekly include sitting pulse, blood pressure, and weight. Height is recorded at baseline and at study end or early termination. In the longer term study (32A), sitting pulse, blood pressure and weight are measured weekly for the first 5 weeks and then monthly. Orthostasis is assessed in Studies 32 and 32A at baseline and the end of Weeks 1,6,10,12, and 24.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The safety data base includes the two pediatric placebo-controlled escitalopram MDD studies (15 and 32), and the longer term escitalopram adolescent study (32A).

7.1.8.3 Standard analyses and explorations of pulse and blood pressure

The mean change from baseline in diastolic blood pressure is greater in the escitalopram group compared to placebo. Otherwise, there are no notable differences in blood pressure and pulse comparing the placebo and escitalopram groups (please refer to Table 7.1.8.3). Orthostasis is

observed to be greater in the escitalopram group than in the placebo group when assessed in Studies 32 and 32A; however, this mean change doesn't appear to be clinically significant as no patient had more than one episode of orthostasis, and only one patient reported accompanying lightheadedness.

Table7.1.8.3 Mean change from baseline in pulse and blood pressure for escitalopram adolescent safety data base (extracted from ISS Table 7.1.2.1.1-1)

Time Point		*Placebo*		*Escitalopram*	
		n	*Mean ± SD*	*n*	*Mean ± SD*
Sitting systolic blood pressure, mm Hg					
Baseline		236	111.1 ± 10.7	231	111.9 ± 12.5
Change	Week 8	203	1.0 ± 11.4	189	–0.9 ± 10.7
	Week 24	40	0.6 ± 9.7	39	2.2 ± 12.2
	End point[a]	236	0.4 ± 11.5	231	–0.8 ± 11.5
Sitting diastolic blood pressure, mm Hg					
Baseline		236	68.4 ± 8.6	231	68.5 ± 8.8
Change	Week 8	203	–0.3 ± 9.2	189	–0.5 ± 8.1
	Week 24	40	0.9 ± 9.9	39	0.3 ± 10.2
	End point[a]	236	–0.1 ± 9.5	231	–0.3 ± 9.2
Sitting pulse rate, bpm					
Baseline		236	75.8 ± 10.3	231	76.3 ± 11.0
Change	Week 8	203	0.4 ± 10.4	189	–1.0 ± 11.8
	Week 24	40	–2.0 ± 10.4	39	–4.1 ± 13.4
	End point[a]	236	–0.6 ± 10.5	231	–1.1 ± 12.2

7.1.8.4 Height /Weight

Growth assessment in the pediatric population can be determined by use of a z-score, defined by the number of standard deviations from the population mean for a specific subject's weight or height given their age and sex. No change in mean z-score would indication that subjects are growing as predicted by CDC growth charts from age adjusted peers. Decreases in z-score would indicate that subjects are lagging behind in growth.

The sponsor states that the z-score changes appear to be similar between treatment groups, indicating that escitalopram doesn't have an identifiable effect on height and weight change in the adolescent population. In his review of z-score data, FDA statistician Dr. Kordzakhia confirms the sponsor's findings. Please see Appendix 3a for a summary table of the pooled short term data z-scores for weight from Studies 15, 18, and 32, and Appendix 3b for data regarding the longer term Study 32A (for details, see Statistical Review and Evaluation by George Kordzakhia, PhD:1/28/09).

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

In the safety data base for adolescent MDD, ECGs are assessed at baseline and at study end/discontinuation of Studies 32 and 15, and at Week 12 during Study 32A. There are no references made to the timing of the ECGs in relation to dosing or food intake.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The safety data base includes the two pediatric placebo-controlled escitalopram MDD studies (15 and 32), and the longer term escitalopram adolescent study (32A).

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

QTc prolongation is noted to be greater in the escitalopram group compared to the placebo group. Even with Bazett's correction (QTcB) and Fredericia's correction (QTcF), QTc prolongation is more prevalent in the escitalopram population (it is questionable if Fredericia's correction is the appropriate correction to use, since there isn't a very significant heart increase observed with escitalopram).

Below, Table 7.1.9.3.1a and Table 7.1.9.3.1b provide summaries of the mean change from baseline of QTc for this safety data base. Because timing of food and drug weren't controlled for during the ECG collections, the interpretation of these findings is limited. These results are consistent with the current label describing an increase in QTc interval of 3.9 msec for Lexapro, compared to placebo.

Table7.1.9.3.1a Mean change from baseline for cardiac parameters for pediatric escitalopram study Studies 32 and 15 (extracted from ISS Table 7.2.2.1.1–1)

Parameter, Units	*Placebo*			*Escitalopram*		
	n	*Baseline, Mean ± SD*	*Change From Baseline to End Point[a], Mean ± SD*	*n*	*Baseline, Mean ± SD*	*Change From Baseline to End Point[a], Mean ± SD*
Ventricular heart rate, bpm	230	71.0 ± 11.0	–0.6 ± 10.8	218	69.6 ± 10.9	0.2 ± 10.9
QRS interval, msec	230	90.2 ± 9.8	–0.3 ± 7.5	218	89.5 ± 9.1	0.8 ± 7.0
PR interval, msec	228	145.3 ± 18.8	1.1 ± 10.5	218	144.7 ± 19.8	1.2 ± 12.2
QT interval, msec	230	376.1 ± 24.9	1.0 ± 22.6	218	378.9 ± 26.9	2.3 ± 22.7
QTcB interval, msec	230	406.4 ± 22.1	–0.7 ± 19.4	218	405.1 ± 21.2	2.9 ± 20.4
QTcF interval, msec	230	395.8 ± 18.2	–0.1 ± 15.4	218	395.9 ± 18.2	2.7 ± 15.5

Table 7.1.9.3.1b Mean change from baseline in weekly mean QTc for adolescent only safety population in Studies 32 and 32A (excerpts from ISS Table 7.2.1.2-1)

Time Point		*Placebo*		*Escitalopram*	
		n	*Mean ± SD*	*n*	*Mean ± SD*
QT interval, msec					
Baseline		156	377.4 ± 24.7	153	377.3 ± 27.0
Change	Week 6	126	1.4 ± 23.7	129	1.9 ± 22.5
	Week 20	40	–2.6 ± 25.4	34	3.6 ± 21.3
	Week 24	22	1.5 ± 26.8	23	7.8 ± 19.2
	End point[a]	156	–2.9 ± 24.0	153	0.4 ± 21.2
QTcB interval, msec					
Baseline		156	405.2 ± 20.5	153	403.9 ± 20.7
Change	Week 6	126	–0.2 ± 16.7	129	3.2 ± 18.7
	Week 20	40	–5.1 ± 18.5	34	0.8 ± 20.3
	Week 24	22	1.0 ± 22.2	23	–3.4 ± 21.4
	End point[a]	156	–1.8 ± 19.6	153	1.7 ± 20.1

Time Point		*Placebo*		*Escitalopram*	
		n	*Mean ± SD*	*n*	*Mean ± SD*
QTcF interval, msec					
Baseline		156	395.5 ± 18.1	153	394.6 ± 17.9
Change	Week 6	126	0.4 ± 14.5	129	2.8 ± 14.7
	Week 20	40	–4.3 ± 16.8	34	1.9 ± 14.4
	Week 24	22	1.0 ± 18.9	23	0.7 ± 17.9
	End point[a]	156	–2.2 ± 16.6	153	1.2 ± 15.2

7.1.9.3.2. Marked outliers and dropouts for ECG abnormalities

There are no dropouts due to ECG abnormalities in this safety data base. 7.1.9.3.2 below summarizes the escitalopram patients with a significant increase in QTc during escitalopram treatment. There are two patients (0091505 and 0303213) with an increased QTc prolongation of > 60 msec; no placebo patients have a clinically significant increase in QTc.

Table 7.1.9.3.2 Summary table of adolescents with significant increase in QTc prolongation during escitalopram treatment for MDD in Studies 32 and 32A.

PATIENT #	AGE/GENDER	BASELINE QT_C (QT_CB/ QT_CF)	QT_C HISTORY DURING STUDY
0323208 (Study 32/32A)	14/M	409/402 msec	Summary: ~ 40 msec ↑QT_C Day 43: 447/441 msec Day 139: 428/431 msec Day 168: 397/398
0091505 (Study 15)	16/F	338/346 msec HR:52 bpm	Summary: ↑QT_C and ↑HR Day 56: 403/382 msec HR: 83 bpm
0303213 (Study 32/32A)	15/F	373/375 msec HR:58	Summary: ↑QT_C and ↑HR Day 42: 440/415 msec HR: 84 bpm Day 98: 413/396 msec HR: 77 bpm

7.1.10 Seizures

A clonic-tonic seizure on Day 47 of Study 32 is reported in one 15 y.o. male escitalopram patient (0383215). This patient completed the study to Day 56, but didn't enroll in the extension study.

7.1.11 Concomitant Medications

For the adolescent safety data base, concomitant medications are used in comparable amounts when comparing the pooled placebo and escitalopram groups. The ISS discusses the higher incidence of abdominal pain, nausea and insomnia reported in the escitalopram compared to placebo, perhaps resulting in the high use of anti-inflammatory and analgesic medications in the escitalopram group. Please see Table 7.1.11 for a summary of concomitant medications in the short term escitalopram studies.

For details regarding the concomitant medications used in Study 32, please refer to the ***Concomitant Medications*** in Section 6.3.1.

Table 7.1.11 Common concomitant medication (≥ 10% of adolescent patients) in short term escitalopram Studies 32 and 15. (extracted from ISS Table 8.3-1)

Preferred Term	*Placebo, n (%) (N = 238)*	*Escitalopram, n (%) (N = 234)*
Patients using ≥ 1 concomitant medication	172 (72.3)	169 (72.2)
Anti-inflammatory and antirheumatic products	79 (33.2)	73 (31.2)
Analgesics	70 (29.4)	69 (29.5)
Antihistamines for systemic use	35 (14.7)	34 (14.5)
Antibacterials for systemic use	32 (13.4)	28 (12.0)
Nasal preparations	26 (10.9)	19 (8.1)

7.1.12 Human Carcinogenicity

No Carcinogenicity studies were submitted with this application

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Studies 32 and 32A both have a down taper period, and the sponsor considers any newly emergent AE during this study period to be a possible withdrawal or rebound effect. The most common newly emergent AE during the taper period for the escitalopram group was irritability (n=2 of 40); for the placebo group, inflicted injury (n=2 of 54) and rhinitis (n=2 of 54) were the most common AE identified.

7.1.14 Human Reproduction and Pregnancy Data

There are no studies on pregnancy in this submission. There are no patients reported to be pregnant while on escitalopram in this escitalopram safety data base.

7.1.15 Assessment of Effect on Growth

Escitalopram doesn't appear to have an identifiable effect on height and weight change in the adolescent population (see Section 7.1.8.4).

7.1.16 Overdose Experience

The following two overdoses reported in the open-label escitalopram Study 32A:

1. An intentional overdose occurred when, on Day 80, a 15 y.o. female ((Patient 0033206) took 40 tablets (a combination of 10 and 20 mg tablets) accumulated throughout the study. The patient was hospitalized for inpatient treatment, and discontinued the study. Other than a moderate headache 1 week after the overdose, no other AEs are reported for this patient.

2. Another overdose termed "accidental" in the ISS describes a 15 y.o. female (Patient 01232040) ingesting six escitalopram 20-mg tablets at one time. At the time of the overdose, the patient reported a moderate headache, thought to be possibly related to study drug. The patient withdrew consent 6 days later, and there is no safety concern reported.

7.1.17 Post-marketing Experience

The sponsor hasn't conducted any post-market pediatric studies beyond those in this submission. According to the sponsor's summary, the post-market adult studies results have been consistent with the current label.

The Medical Dictionary for Regulatory Activities (MedDRA) is used for the escitalopram spontaneous post market reports (or spontaneous adverse events-SAE). Tables 7.1.17a summarizes the incidence of AEs reported, and Table 7.1.17b lists events identified in the pediatric population compared to adults. For the spontaneous pediatric escitalopram reported by the sponsor, the following are of note:

1. Many escitalopram pediatric SAE events may be due to in utero exposure, and, thus, are categorized as congenital anomalies or perinatal complications;
2. The SAE of children (<12 y.o.) exposed to escitalopram, describe overdose and accidental overdose in a higher percentage of total reports than in the adult age group;
3. The SAE of adolescents (12-17 y.o.) suicide attempt, overdose, and intentional overdose comprise a higher percentage of the total reports than in the adult age group.

Table 7.1.17a Total spontaneous reports for escitalopram and citalopram from 10/21/02 to 12/31/07 (extracted from ISS Table 9.2.3-1)

Product	*Child*[a]	*Adolescent*[b]	*Adult*[c]	*Unspecified*	*Total*
Escitalopram	719	1443	26,812	4921	33,895
Citalopram	599	759	21,111	3959	26,428
Total	1318	2202	47,923	8880	60,323

a *Child* defined as aged 0 to 11 years.
b *Adolescent* defined as aged 12 to 17 years.
c *Adult* defined as 18 years and older.

Table 7.1.17b Escitalopram spontaneous AEs in pediatric population compared to adults from 10/21/02 to 12/31/07 (extracted from ISS Table 9.2.4.1-1)

Age Group[a]	*Events Only Seen in Age Group When Compared With Adults and Reported More Than Twice (No. of Reports)*	*Events Seen as a Lower Percentage of Total Reports (> 1% Difference) in Age Group When Compared With Adults (% Difference)*	*Events Seen as a Higher Percentage of Total Reports (> 1% Difference) in Age Group When Compared With Adults (% Difference)*
Child	Premature baby (9)[b] Neonatal jaundice (4)[b] Atrioventricular septal defect (3)[b] Low Apgar score (3)[b]	Nausea (4.3) Insomnia (3.4) Fatigue (2.6) Dizziness (2.5) Headache (2.4) Anxiety (1.8) Diarrhea (1.4) Hyperhidrosis (1.4) Tremor (1.2)	Overdose (42.2) Accidental overdose (5.2)
Adolescent	None	Nausea (3) Insomnia (2.9) Dizziness (1.8) Diarrhea (1.5) Headache (1.4) Fatigue (1.4) Anxiety (1.2) Hyperhidrosis (1)	Suicide attempt (12) Overdose (10) Intentional overdose (6.8) Suicidal ideation (1)

a The age groups were defined as follows: child = 0 to 11 years of age; adolescent = 12 to 17 years of age; adult = 18 years and older.
b These events were reported in newborns who were exposed to escitalopram during pregnancy.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The escitalopram safety data base for treatment of adolescents with MDD includes the following:

1. **Study 32**, a multicenter, 8 week double-blind, placebo-controlled, flexible dose escitalopram (10-20 mg/d) study in adolescents diagnosed with MDD with 2 treatment groups: placebo (n=155) and escitalopram (n=157).

2. **Study 15**, a multicenter, 8 week double-blind, placebo-controlled, flexible dose escitalopram (10-20 mg/d) study in pediatric (6-17 y.o.) patients diagnosed with MDD with 2 treatment groups: placebo (n=133 includes 81 adolescents) and escitalopram (n=131 includes 79 adolescents).

3. **Study 32A,** a multicenter, longer term escitalopram study in adolescents diagnosed with MDD. The following major design changes were implemented after the start of the study: a) primary outcome variable (from time to discontinuation → Δ CDRS from baseline);
   b) 24 weeks open label → 16 weeks placebo-controlled

The sponsor presents their safety data primarily in the adolescent population in the following categories:

1. The **escitalopram** safety data base is comprised of a pooling of data from the two 8 week, placebo controlled studies, Study **32** (ages 12-17) and Study **15** (limited to adolescents within the study population of ages 6-17). Also included in this pooling is the extension Study **32A (**ages 12-17), which began as open label and later evolved into a placebo controlled design.

2. Data from the **citalopram** studies are presented separately and not pooled do to differences in study duration, in patient/out patient status, and imbalance in the number of adolescent patients. The two **citalopram**, placebo controlled studies are Study **18** (outpatient, 8 weeks; ages 7-17) and Study **94404** (in patient and outpatient, 12 weeks; ages 13-18). **Citalopram** open label, longer term extension studies included Study **20** (extension of 18; n=5 adolescents) and Study **19** (extension of 07; n=57 adolescents).

A total of **988** pediatric patients received ≥1 dose of study drug; of these, **764** patients were between ages 12-17 y.o. and **36** patients aged 18 y.o. (from study 94404). Therefore, the sponsor

counts a total of 800 adolescent patients in the escitalopram/citalopram safety data base with the following breakdown:

placebo: n=387
escitalopram: n=234
citalopram: n=169

7.2.1.2 Demographics

In the escitalopram adolescent safety data base (Studies 15 and 32), there are 135 females (57.7%) and 99 males (42.3%) with a mean age of 14.6years (± 1.6) exposed to escitalopram. The majority of patients exposed to escitalopram are Caucasian (n=162 or 72.2%); other escitalopram exposures include 42 (17.9%) African Americans, 4 (1.7%) of Asian decent, and 19 (8.1%) "other.

7.2.1.3 Extent of exposure (dose/duration)

A total of 210 patients (181 adolescents) received **escitalopram** for at least 8 weeks, and 53 patients (all adolescents) received **escitalopram** for at least 24 weeks; 211 patients (154 adolescents) received **citalopram** for at least 8 weeks, and 66 patients (30 adolescents) received **citalopram** for at least 24 weeks. The sponsor concludes that the **escitalopram/citalopram** safety data base includes 83 adolescents (of 119 pediatric patients) who were exposed for up to 24 weeks of **escitalopram** or **citalopram**.

Doses for escitalopram are either 10 or 20 mg daily. Of the 154 intent-to-treat escitalopram patients in Study 32, 54 patients received 10mg on their last visit, and 100 patients received 20mg on their last visit.

Please see Tables 7.2.1.3a and 7.2.1.3b, below, for sponsor tables summarizing escitalopram exposure.

Table 7.2.1.3a Duration of treatment in escitalopram double-blind clinical Studies 32, 15 and 32A (extracted from ISS Table 4.2.3.1.1-1)

	Adolescents		*All Patients*	
	Placebo (N = 238)	*Escitalopram (N = 234)*	*Placebo (N = 290)*	*Escitalopram (N = 286)*
Overall duration of treatment, d (%)				
1-28	20 (8.4)	32 (13.7)	25 (8.6)	35 (12.2)
29-56	93 (39.1)	77 (32.9)	121 (41.7)	110 (38.5)
57-84	60 (25.2)	61 (26.1)	79 (27.2)	77 (26.9)
> 84	65 (27.3)	64 (27.4)	65 (22.4)	64 (22.4)
Short-term exposure, duration 1 to 56 d				
n	113	109	146	145
Mean ± SD	45.9 ± 15.4	41.8 ± 17.4	46.5 ± 15.3	43.6 ± 16.6
Median (min, max)	55.0 (5, 56)	54.0 (1, 56)	55.0 (2, 56)	54.0 (1, 56)
Overall exposure, d				
n	238	234	290	286
Mean ± SD	83.4 ± 59.5	80.1 ± 57.9	77.9 ± 55.4	75.1 ± 53.7
Median (min, max)	57.0 (5, 235)	57.0 (1, 243)	56.0 (2, 235)	56.0 (1, 243)
Patient-years	54.4	51.3	61.9	58.7

7.2.1.3b Dosing in escitalopram placebo-controlled clinical Studies 32, 32A, and 15 (extracted from ISS Table 4.2.3.1.1-2)

	Adolescents			*All Patients*		
	Placebo (N = 238)	*Escitalopram (N = 234)*		*Placebo (N = 290)*	*Escitalopram (N = 286)*	
	Tablets	**Tablets[a]**	**mg**	**Tablets**	**Tablets[a]**	**mg**
Overall daily dose						
Mean ± SD	1.4 ± 0.4	1.3 ± 0.4	13.3 ± 3.3	1.3 ± 0.4	1.3 ± 0.4	13.0 ± 3.2
Median (min, max)	1.4 (0.7, 2.0)	1.0 (0.6, 2.0)	13.8 (5.9, 19.1)	1.0 (0.7, 2.0)	1.0 (0.6, 2.0)	13.5 (5.9, 19.1)
Distribution of final daily dose, n (%)						
1 Tablet	69 (29.0)	96 (41.0)	—	91 (31.4)	118 (41.3)	—
2 Tablets	169 (71.0)	137 (58.5)	—	199 (68.6)	167 (58.4)	—

Note: 1 tablet=10 mg escitalopram; 2 tablets=20 mg escitalopram

7.2.1.4 Literature

The sponsor conducted a literature search using the electronic databases MEDLINE, BIOSIS, and EMBASE for escitalopram and citalopram in the pediatric population; the credentials of the

person doing the research isn't specified in there submission. The sponsor describes 1870 unique publications discussing some aspect of safety issues related to escitalopram. Unusual events published include emergence of tics (escitalopram), dystonic rabbit syndrome (escitalopram and citalopram), EPS (escitalopram), anaphylaxis with oculogyric dystonia (escitalopram), and enuresis (citalopram). The sponsor summarizes the vast amount of literature regarding suicide in the pediatric population in terms of anti-depressant use; however, the details of this topic are beyond the scope of this review.

7.2.3 Adequacy of Overall Clinical Experience

There are too few non-Caucasians included in the safety data base for escitalopram. Also, most of the safety data base is comprised of adolescents (12-17). There is very little escitalopram data in children 6-12 y.o. Considering the off-label use for younger kids, and that written requests for MDD include the pediatric population aged 6-17, there may be a need to have controlled efficacy and safety data on children aged 6 to 12 y.o.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There are no special animal and/or in vitro testing accompanying this submission.

7.2.5 Adequacy of Routine Clinical Testing

This application focuses on the adolescent population. There is a small number of patients younger than 12 y.o. exposed to escitalopram in a controlled safety data base despite off-label use.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There are no special studies conducted for the pediatric MDD indication.

7.2.8 Assessment of Quality and Completeness of Data

The sponsor presented an adequate application that summarized data in an organized fashion.

7.2.9 Additional Submissions, Including Safety Update

The safety update dated September 19, 2008, covers the period of January 1 to May 23, 2008. The only studies completed during that period are in the adult population, and findings are consistent with the current label. The spontaneous post-market reporting summary notes many reports of neonates exposed to escitalopram and citalopram in utero. This drug is labeled as a Pregnancy Category C with a note of risks during pregnancy. FDA Maternal Health Team is reviewing and recommending amendments to the Lexapro label to include information from some of these reports.

When comparing adult spontaneous reports to those made of children and adolescents, the pediatric patients are reported to have a higher incidence of overdose and suicidality. Please see Appendix 4, for the sponsor's summary table comparing adult and pediatric spontaneous reports and a listing of events for this safety reporting period. As part of class labeling, escitalopram labeling has a bold warnings regarding pediatric suicide.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Many of the safety concerns reported in this supplemental NDA are addressed in the current escitalopram labeling.

There appears to be a signal (although, not pronounced) of suicidal gesture/attempts in this escitalopram safety data base, in addition to many spontaneously report adverse events identified through the sponsor's search. It is noted that this issue is already recognized by an anti-depressant class label WARNING of increase rates of suicide attempts in children/adolescents/young adults treated with anti-depressants.

Common AEs occurring with greater frequency in the escitalopram group compared to placebo in acute studies include the following: headache, abdominal pain, nausea, and insomnia; headache was identified as the most common treatment emergent AE in the adolescent escitalopram data base. In the longer term escitalopram study, diarrhea and urinary tract infections (UTI) are also considered common AEs (note: UTI was reported in ≥ 5 % of escitalopram patients with an incidence of ≥ 2 times observed in placebo patients).

Events observed in the escitalopram adolescent safety data base already addressed in the adult labeling include: elevated LFTs, orthostasis, and QTc prolongation of 3-4 msec with a couple of outliers with a > 60 msec increase.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the proposed labeling, the sponsor recommends 10 mg escitalopram once daily that as the initial dose of Lexapro® to treat adolescents with MDD. After referring to the flexible (10-20 mg daily) dose clinical studies, the labeling states that an increase in dose up to 20 mg should occur after a minimum of 3 weeks at the 10 mg dose.

8.2 Drug-Drug Interactions

There is no new information regarding drug-drug interactions in this supplement. As stated in the marketed labeling, the concomitant use of escitalopram with MAOIs is contraindicated. As an SSRI, escitalopram should be used with caution with drugs that affect hemostasis (e.g. NSAIDs, aspirin, warfarin), and other serotonergic drug (e.g. triptans, linezoilid, lithium, tramadol, St. John's Wort, other SSRIs, SNRIs, and typtophan). Caution is also recommended when co-administering escitalopram with any CNS drug or alcohol.

8.3 Special Populations

There is no new information in this supplement regarding special populations.

For **special populations**, the labeling recommends the dose of 10 mg/day in most elderly patients and patients with hepatic impairment, and that escitalopram should be used with caution in patients with severe renal impairment. There is a precaution that neonates exposed in-utero in the late third trimester may develop complications requiring prolonged hospitalization, respiratory support, and tube feeding.

8.4 Pediatrics

This application is limited to escitalopram treatment of MDD for the adolescent population. There is little safety data in children younger than 12 y.o., and the one study that included this younger age group has negative efficacy results.

8.5 Advisory Committee Meeting

No advisory committee meeting was held to discuss this adolescent MDD claim for escitalopram.

8.6 Literature Review

In the sponsor's literature review, some unusual events reported include emergence of tics (escitalopram), dystonic rabbit syndrome (escitalopram and citalopram), EPS (escitalopram), anaphylaxis with oculogyric dystonia (escitalopram), and enuresis (citalopram).

8.7 Post-marketing Risk Management Plan

The sponsor is encouraged to monitor post-marketing suicidal tendencies/events; especially given that this drug will now be indicated for the high risk group of adolescents.

9 OVERALL ASSESSMENT

9.1 Conclusions

There is one positive escitalopram placebo controlled study, and one positive citalopram study that support the labeling claim that escitalopram is effective in the treatment of MDD in the adolescent population. The escitalopram adolescent safety data base appears to be consistent with the current label for escitalopram, containing no unexpected events.

9.2 Recommendation on Regulatory Action

It is recommended that escitalopram be approved for the indication of MDD in the adolescent population. The dosing of 10 mg and 20mg escitalopram appear to be effect and safe in this population. The sponsor's proposed dosing of beginning at 10mg and, if necessary, titrating to 20 mg after 3 weeks, is consistent with the prudent pediatric dosing concept of "start low and go slow."

When escitalopram receives the labeling claim of acute MDD treatment in adolescents, the label may be eligible to extend this adolescent claim to longer term maintenance MDD treatment by extrapolation of the adult MDD data.

Once escitalopram is labeled for adolescents, it is recommended that the sponsor also include a section entitled **"Need for Comprehensive Treatment Program,"** modeled after this section in the labels for stimulant use in ADHD (an indication that traditionally was solely in pediatrics). This could highlight to clinicians that medication treatment is just one aspect of the effective treatment of adolescents suffering with MDD. Many clinicians (i.e. pediatricians and general practitioners) now prescribing medication to adolescents suffering with MDD, may not be specifically trained to understand the importance that talking therapies, engaging the family and adjusting school programs have in treating psychiatric illnesses in the pediatric population. This need for a "Comprehensive Treatment Program" becomes even more important when considering the elevated suicidality in this vulnerable adolescent population.

9.3 Recommendation on Post-marketing Actions

9.3.1 Risk Management Activity

It is important that the sponsor continue to monitor treatment emergent suicidality in this vulnerable population of adolescents suffering with major depressive disorder.

9.3.2 Required Phase 4 Commitments

Because escitalopram will obtain labeling for the adolescent population with MDD, it is likely that clinicians will increase their use in younger children off-label. It would be helpful if the sponsor would power a study to assess the efficacy of escitalopram in this younger population.

9.3.3 Other Phase 4 Requests

It is curious that a subgroup analysis revealed that patients categorized as African American did not demonstrate an improvement in MDD symptoms with escitalopram treatment. This observation and the fact that the escitalopram data base was composed primarily of Caucasians (>70%) would suggest that studying adolescents in varied racial background would offer clinicians better guidance for treatment decisions for individual patients.

9.4 Labeling Review

The final labeling for this application is the first escitalopram (Lexapro ®) label in the PLR format. Therefore, input is need from all disciplines to ensure continuity of labeling information into the PLR labeling format.

Conceptually, the labeling needs to reflect that most of the pediatric safety data base is in adolescents (12-17) with very little exposure in children (6-12). It also needs to be clear that efficacy for escitalopram is established by one escitalopram adolescent study and one citalopram pediatric study in which the positive results were primarily in the adolescent group.

As discussed in Section 9.2, above, it is recommended that the sponsor add a section entitled "**Need for Comprehensive Treatment Program**." This section can be used to emphasize the need to engage the family and school environment in a complete treatment plan to treat adolescents suffering with MDD, and that medication treatment is just one aspect of effective treatment.

The following are some specific recommendations in response to the sponsor's proposed labeling for this submission:

A. Summary Page:

1. It is unclear how far back the RECENT MAJOR CHANGES should go back. The sponsor's proposed labeling does not include any changes before 2008.
2. In the INDICATIONS AND USAGE section, the listing of "Treatment of Generalized Anxiety Disorder" needs to specify that this is for **adults only**.

B. INDICATIONS AND USAGE Section:

1. Under Section 1.1. Major Depressive Disorder, the entire proposed section should be replaced with the following language:

(b) (4)

(b) (4)

2. Under 1.2 Generalized Anxiety Disorder the entire proposed section should be replaced with the following language:

LEXAPRO is indicated for the treatment of Generalized Anxiety in adult patients. *[see Clinical Studies (14.X)]*.

C. In Section 2 DOSAGE AND ADMINISTRATION:

1. Mention of the lower dose in patients with hepatic disorders earlier in this section would be helpful.
2. Under Maintenance Treatment, the sponsor may add that MDD maintenance treatment for adolescents may be extrapolated from adult efficacy data.
3. Generalized Anxiety Disorder heading needs to add "in adults."
4. Special Populations section should be moved to the last listing of this section (b) (4).

D. In Section 5 WARNINGS AND PRECAUTIONS:

1. In Section 5.1 Clinical Worsening and Suicide Risk, the following language should be added to the end of this section:

(b) (4)

E. Section 6.2: Under MDD Pediatrics: In addition to the sponsor's proposal, headache is identified as the most common treatment emergent AE in the adolescent escitalopram data base. UTI is reported in ≥ 5 % of escitalopram patients with an incidence of ≥ 2 times observed in placebo patients.

F. Section 14 CLINICAL STUDIES

1. Study 18, the citalopram 8 week study in children and adolescents needs to be described in this section to explain that this was one of the two required studies used to support the efficacy of escitalopram in the adolescent population.
2. The longer term escitalopram study has several design flaws and the results were uninterpretable; therefore, for the purposed of efficacy, it is inappropriate to include it in labeling. The sponsor may explain that they have obtained a longer term maintenance claim in the adolescent population due to extrapolation of adult efficacy data.

G. In Section 14.2 GAD: specify that this indication is in **adults only**.

10 APPENDICES

Appendix 1

Schedule of Events for Study 32 (sponsor amended version dated 4/27/07)

			End of Double-Blind Treatment Week							*Double-Blind Down Taper*
	Screening		*Baseline*	*1*	*2*	*3*	*4*	*6*	*8*	*9*
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[1]**	**10**
Informed Assent and Consent (Patient)	x									
Informed Consent (Caregiver)			x							
Inclusion / Exclusion (Patient)	x	x	x							
Inclusion Criteria (Caregiver)			x							
Medical History (Patient)	x									
Psychiatric History (Patient)	x									
Background Information of the Caregiver and Family (Caregiver)			x							
Physical Examination	x[2]								x	
Clinical Laboratory Determinations	x[2]							x[3]		
Serum Pregnancy Test	x[2]							x[3]		
Thyroid Function Test	x[2]									
Urine Drug Screen	x[2]							x[3]		
ECG	x[2]			x				x[3]		
Plasma Sample								x[3]		
Vital Signs	x[2,4]		x[5]	x[5]	x	x	x	x[3,5]	x[4]	
KBIT	x									
K-SADS-PL	x	x								
CDRS-R	x		x	x	x	x	x	x	x	
CGI-S			x	x	x	x	x	x	x	
CGI-I				x	x	x	x	x	x	
CGAS			x				x		x	
SIQ-JR	x		x	x			x		x	
MC-SSRS	x		x	x	x	x	x	x	x	x
AEs		x	x	x	x	x	x	x	x[6]	x[6]
Concomitant Medications	x	x	x	x	x	x	x	x	x	x
Drug Dispensing		x	x	x	x	x	x	x	x[7]	
Drug Return			x	x	x	x	x	x	x	x
Final Evaluation									x[8]	x[8]
Resource Utilization and Productivity Instrument (Caregiver)			x				x		x	
Family Interaction Instrument (Caregiver)			x				x		x	
General Health Instrument (Caregiver)			x				x		x	
Follow-Up Questionnaire (Caregiver)[9]							x		x	

			End of Double-Blind Treatment Week							Double-Blind Down Taper
	Screening		Baseline	1	2	3	4	6	8	9
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[1]**	**10**
Informed Assent and Consent	x									
Inclusion / Exclusion	x	x	x							
Medical History	x									
Psychiatric History	x									
Physical Exam	x[2]								x	
Clinical Laboratory Determinations	x[2]							x[3]		
Serum Pregnancy Test	x[2]							x[3]		
Thyroid Function Test	x[2]									
Urine Drug Screen	x[2]							x[3]		
ECG	x[2]			x				x[3]		
Plasma Sample								x[3]		
Vital Signs	x[2,4]		x[5]	x[5]	x	x	x	x[3,5]	x[4]	
KBIT	x									
K-SAD-PL	x	x								
CDRS-R	x		x	x	x	x	x	x	x	
CGI-S			x	x	x	x	x	x	x	
CGI-I				x	x	x	x	x	x	
CGAS			x				x		x	
SIQ-JR	x		x	x			x		x	
AEs		x	x	x	x	x	x	x	x[6]	x[6]
Concomitant Medications	x	x	x	x	x	x	x	x	x	x
Drug Dispensing		x	x	x	x	x	x	x	x[7]	
Drug Return			x	x	x	x	x	x	x	x
Final Evaluations									x[8]	x[8]

1. All Visit 9 assessments to be completed for patients who discontinue prior to Week 8.
2. May be performed at the Investigator's discretion at Visit 2.
3. **To be performed as part of Early Termination Visit for patients who discontinue prior to Visit 8 only.**
4. Height is recorded at Visit 1 and Visit 9 (or Early Termination Visit), only.
5. **Standing blood pressure and heart rate measurements to be recorded in addition to seated measurements.**
6. Clinical findings upon termination must be followed until the condition returns to pre-study status or can be explained as unrelated to study drug. If necessary, a follow-up visit should be scheduled within 28 days of termination. Applicable for patients not entering the extension study.
7. For patients entering double-blind down taper.
8. For patients completing double-blind down taper, otherwise completed at Visit 9.

Appendix 2

Patients with PCS post-baseline values in LFTs in escitalopram safety data base
(extracted from ISS Table 6.3.1-3)

Study	*Patient ID (Age, y/Sex)*	*Parameter (Reference Range)*	*Laboratory Values*				
Placebo							
SCT-MD-32	0153208 (15/M)		*Baseline (11/16/05)*	*End Point (01/04/06)*		*Follow-Up (01/20/06)*	*Follow-Up (01/27/06)*
		Alk Phos (52-171 U/L)[a]	157	136		147	151
		ALT (5-30 U/L)	22	***106***		57	40
		AST (10-38 U/L)	15	***115***		71	38
		Bilirubin, total (0-19 µmol/L)	5	14		7	12
SCT-MD-32A	0303221 (14/M)		***SCT-MD-32***		***SCT-MD-32A***		
			Baseline (02/19/07)	*End Point (04/16/07)*	*Day 141 (07/23/07)*	*Day 155 (08/06/07)*	*End Point (08/20/07)*
		Alk Phos (74-390 U/L)	179	176	162	164	149
		ALT (5-30 U/L)	25	22	21	23	17
		AST (10-38 U/L)	28	27	26	25	22
		Bilirubin, total (0-19 µmol/L)	14	17	***36***	32	26
Escitalopram							
SCT-MD-15	0081501 (13/F)		*Baseline (02/07/03)*	*End Point (04/11/03)*		*Follow-Up (04/16/03)*	*Follow-Up (05/29/03)*
		Alk Phos (50-162 U/L)	184	142		148	180
		ALT (5-20 U/L)	17	44		28	17
		AST (10-31 U/L)	30	***97***		38	29
		Bilirubin, total (0-19 µmol/L)	5	5		5	3

Study	*Patient ID (Age, y/Sex)*	*Parameter (Reference Range)*	*Laboratory Values*					
SCT-MD-15	0231508 (13/F)		*Baseline (05/07/03)*				*End Point (07/10/03)*	
		Alk Phos (50-162 U/L)	147				139	
		ALT (5-20 U/L)	13				12	
		AST (10-31 U/L)	23				19	
		Bilirubin, total (0-19 µmol/L)	29				***38***	
Open-label escitalopram								
SCT-MD-32A	0153206[b] (15/F)		***SCT-MD-32***		***SCT-MD-32A***			
			Baseline (08/03/05)	*End Point (09/21/05)*	*Day 99 (11/16/05)*	*Day 136 (12/23/05)*	*Day 155 (01/11/06)*	*End Point (03/21/06)*
		Alk Phos (47-119 U/L)[c]	99	94	94	99	105	103
		ALT (5-20 U/L)	12	6	11	11	11	15
		AST (10-29 U/L)[c]	15	13	17	***180***	16	17
		Bilirubin, total (0-19 µmol/L)	26	29	29	21	17	19

Appendix 3a

Pooled analysis of weight z-scores for short term placebo-controlled Studies 15, 18, and 32.
(extracted for Statistical Review and Evaluation by George Kordzakhia, PhD: draft, 1/2009).

Pooled	**Placebo**		**Citalopram**		**Escitalopram**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Overall	373		89		282	
Baseline		1.20 (1.09)		1.11 (1.25)		1.13 (1.14)
Change		0.04 (0.125)		0.00 (0.17)		0.03 (0.129)
Male	166		42		124	
Baseline		1.16 (1.13)		1.13 (1.28)		1.04 (1.22)
Change		0.05 (0.14)		0.03 (0.19)		0.04 (0.13)
Female	207		47		158	
Baseline		1.23 (1.06)		1.10 (1.23)		1.21 (1.07)
Change		0.04 (0.11)		-0.04 (0.15)		0.02 (0.13)

Appendix 3b

Mean change from baseline in weight z-scores for Study 32/32A

(extracted for Statistical Review and Evaluation by George Kordzakhia, PhD: draft, 1/2009)

Study 32/32A	**Placebo**		**Escitalopram**	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Overall	82		83	
Baseline		1.37 (1.17)		1.10 (1.20)
Change		0.08 (0.15)		0.09 (0.21)
Male	38		31	
Baseline		1.42 (1.35)		1.52 (1.40)
Change		0.10 (0.18)		0.13 (0.17)
Female	44		52	
Baseline		1.34 (0.99)		0.84 (0.99)
Change		0.06 (0.11)		0.06 (0.23)
	Placebo+Open Label Escitalopram		**Escitalopram+Open Label Escitalopram**	
Baseline	18	1.02 (0.95)	19	1.54 (1.26)
Change	18	-0.01 (0.11)	19	0.04 (0.14)

Appendix 4

Sponsor's Summary Table comparing adult and pediatric patients post-marketing spontaneous adverse event reports (extracted from Safety Update dated 8/19/08)

Table 6.1-1. Total Adverse Events for Escitalopram and Citalopram by Age Group

Product	*Child (0-11 y)*	*Adolescent (12-17 y)*	*Adult (18 y and Older)*	*Unspecified*	*Total*
Escitalopram	753	1494	28,417	5264	35,928
Citalopram	621	776	21,661	4118	27,176
Total	**1374**	**2270**	**50,078**	**9382**	**63,104**

Table 6.1.1-2. Citalopram Adverse Events in Children and Adolescents Compared With Adults

Age Group[a]	*Events Only Seen in Age Group When Compared With Adults and Reported More Than Twice (No. of Reports)*	*Events Seen as a Lower Percentage of the Total Reports (> 1% Difference) in the Age Group When Compared With Adults (% Difference)*	*Events Seen as a Higher Percentage of the Total Reports (> 1% Difference) in the Age Group When Compared With Adults (% Difference)*
Child	Drug withdrawal syndrome neonatal (12)[b] Apgar score low (7)[b] Neonatal respiratory distress syndrome (6)[b] Neonatal disorder (6)[b] Congenital anomaly (5)[b] Infantile apnoeic attack (4)[b] Growth retardation (4)[b] Patent ductus arteriosus (4)[b] Ventricular septal defect (4)[b] Jaundice neonatal (4)[b] Congenital eye disorder (3)[b] Neonatal asphyxia (3)[b] Neonatal aspiration (3)[b] Talipes (3)[b] Neonatal respiratory depression (3)[b] Respiratory disorder neonatal (3)[b] Congenital hand malformation (3)[b] Hyperbilirubinaemia neonatal (3)[b]	Nausea (2.2) Hyponatraemia (1.5) Headache (1.3) Insomnia (1.1) Hyperhidrosis (1.0)	Accidental overdose (1.3) Drug exposure during pregnancy (1.4) Hypertonia (1.1) Hypotonia (1.1) Premature baby (2.4)
Adolescent	None	Diarrhoea (1.1) Nausea (1.1)	Intentional overdose (1.5) Overdose (2.8) Convulsion (2.1) Aggression (1.1) Intentional self-injury (1.1) Suicidal ideation (1.2) Suicide attempt (3.0)

a The age groups were defined as follows: child, 0 to 11 years of age; adolescent, 12 to 17 years of age; adult, 18 years and older.

b Events reported in newborns who were exposed to citalopram during pregnancy.

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/s/

Roberta Glass
1/29/2009 01:19:03 PM
MEDICAL OFFICER

Ni Aye Khin
2/17/2009 09:19:24 AM
MEDICAL OFFICER
I agree with Dr. Glass that this set of NDA supplements should be considered for approval; see memo to file for additional comments.

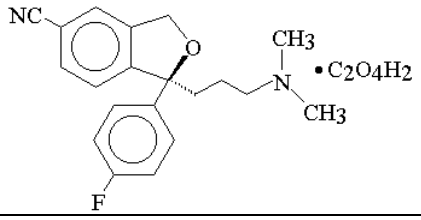
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1

	1. ORGANIZATION ONDQA/DPE/Branch VII	2. NDA NUMBER 21-323 21-365
3. NAME AND ADDRESS OF APPLICANT (*City and State*) Forest Laboratories, Inc. Harborside Financial Center Plaza Three, Suite 602 Jersey City, NJ 07311.		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG Lexapro (21-323) Lexapro (21-365)	7. NONPROPRIETARY NAME Escitalopram oxalate	SE5-030 05-22-2008 SE5-021 05-22-2008
8. SUPPLEMENT PROVIDES FOR: the acute treatment of adolescent (12-17 years) patients with Major depressive disorder.		9. AMENDMENTS DATES 08-13-2008
10. PHARMACOLOGICAL CATEGORY Antidepressant	11. HOW DISPENSED RX ✓ OTC	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) Tablets (21-323) Oral Solution (21-365)	14. POTENCY 5 mg, 10 mg and 20 mg 5 mg/mL	
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT S-(+)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ M. Wt. 414.40 		16. RECORDS AND REPORTS CURRENT YES___ NO REVIEWED YES__ NO

17. COMMENTS

The above two efficacy supplements were submitted for the acute treatment of adolescent (12-17 years) patients with major depressive disorder. The applicant has cross-referenced the CMC information that was submitted in the original NDA (21-323). No changes are proposed to the description, dosage and administration and how supplied sections of the labeling. The applicant has submitted a claim for categorical exclusion from filing an EA document under 21 CFR 25.31 (b). The applicant's claim is found to be acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Provided information is found to be adequate. The above two supplements are recommended for approval from the standpoint of chemistry, manufacturing and controls.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Nallaperumal Chidambaram, Ph.D.		09-12-2008

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: R. Grewal HFD-130	Branch Chief: James D. Vidra Ph.D.

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

/s/

Nallaperumal Chidambaram
9/12/2008 02:08:20 PM
CHEMIST

Jim Vidra
9/12/2008 02:13:10 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-323/ S-030, S-031; 21-365/ S-021, S-022.
Drug Name:	Lexapro (Escitalopram)
Indication(s):	Major Depressive Disorder
Applicant:	Forest Research Institute
Date(s):	Initial submission date: May 22, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	George Kordzakhia, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D; H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Roberta Glass, M.D., Reviewer Ni Khin , M.D., Team Leader
Project Manager:	Ms. Renmeet Grewal

Keywords: clinical studies, NDA review

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1.1 CONCLUSIONS AND RECOMMENDATIONS

Study SCT-MD-32

In the primary analysis of CDRS-R Total score, adolescent patients (12 to 17 years of age) with Major Depressive Disorder on escitalopram 10-20mg/d were observed to show statistically significant improvement over patients in the placebo treatment group.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score. Whether the magnitude of the observed treatment difference is clinically relevant is deferred to the clinical review team.

Study SCT-MD-32a

In this reviewer's opinion, this trial does not provide interpretable evidence for the long-term efficacy (maintenance) claim.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted results of two efficacy and safety studies: Study SCT-MD-32 and Study SCT-MD-32a (extension of Study SCT-MD-32).

Study SCT-MD-32 was an 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study of the safety and efficacy of escitalopram in the treatment of adolescent patients (12-17 years of age) with Major Depressive Disorder. The escitalopram dosage was 10 mg/d for the first three weeks of double-blind treatment. The dosage could be increased to 20 mg/d by the investigator at the end of Treatment Week 3 (Visit 6) or Treatment Week 4 (Visit 7). Patients who completed the 8-week double-blind treatment period of Study SCT-MD-32 were eligible to enter the extension study, SCT-MD-32A, for an additional 16-24 weeks of treatment. During double-blind treatment in Study SCT-MD-32A, patients were to receive the same daily dosage of the blinded study drug they were receiving at Week 4 (Visit 7) of Study SCT-MD-32.

A total of 316 patients were randomized to receive double-blind study drug in Study SCT-MD-32; 312 patients received at least one dose of double-blind study drug (Safety Population); and 311 patients had at least one postbaseline CDRS-R assessment (ITT Population). A total of 133 (84.2%) placebo patients and 126 (79.7%) escitalopram patients completed 8 weeks of double-blind treatment, and 165 patients (82 placebo, 83 escitalopram) continued into the double-blind treatment of the extension study, SCT-MD-32A. Overall, 40 (25.3%) patients in the placebo group and 37 (23.4%) patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A.

1.3 STATISTICAL ISSUES AND FINDINGS

Study SCT-MD-32

Escitalopram treatment group (10mg/d to 20mg/d) was statistically superior to placebo in mean change from baseline to Week 8 in CDRS-R Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with treatment group and study center as factors, and the baseline CDRS-R total score as a covariate was 0.022.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score at Week 8. The p-value of the ANCOVA LOCF analysis was 0.008. Whether the magnitude of the observed treatment difference (LSMD=-0.3) is clinically relevant is deferred to the clinical review team.

No statistical issues were found.

Study SCT-MD-32a

The primary efficacy endpoint was change from the baseline of Study 32 to the endpoint visit of Study 32a. Note that when the data of acute phase are combined with long-term phase, then the maintenance effect is confounded with acute effect.

Study SCT-MD-32A was initially an open-label extension but subsequently amended to a 24-week double-blind extension, and as the study progressed was further changed to a 16-week double-blind extension. Thus, patients enrolled in the double-blind extension had different exposure times.

Also, the patient population for study 32a consisted of completers of Study 32 who chose to continue into the extension study. Of the 259 patients who completed Study SCT-MD-32, 202 chose to enroll in Study SCT-MD-32A; 165 of these patients continued into the double –blind treatment and received the same blinded study drug they were receiving in Study SCT-MD-32. Thus, treatment groups in Study 32a do not represent random samples of the screened patient population. Typically, to assess maintenance effect patients should be stabilized on the studied medication and then randomized to placebo and drug treatment groups before entering into maintenance phase.

Of the 202 patients who entered the extension study (165 double-blind, 37 open-label), approximately 50% (103/202) prematurely discontinued. The most common reason for premature discontinuation during the extension study was insufficient therapeutic response (35 patients [18 placebo, 16 escitalopram, 1 open-label escitalopram]). Overall, only 25.3% of patients in the placebo group and 23.4% of patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A. For any trial with a very high dropout rate, it is always questionable whether the data can be interpretable.

2 INTRODUCTION

2.1 OVERVIEW

The sponsor intends to claim for acute treatment based on one placebo-controlled study with escitalopram in adolescents, 12 to 17 years (Study SCT-MD-32), and one placebo-controlled study with citalopram (Study CIT-MD-18, submitted earlier) in children and adolescents, 7 to 17 years (in accordance with agreements with the FDA). The primary efficacy parameter in these two studies was the change from baseline to the end of Week 8 in the Children's Depression Rating Scale–Revised (CDRS-R) score using the last-observation-carried-forward (LOCF) approach. Based on the sponsor's overview of clinical efficacy, in a previous double-blind acute treatment 8-week study (SCT-MD-15) in pediatric patients (6-17 years old) with MDD, escitalopram 10-20 mg/d did not demonstrate statistically significantly greater improvement than placebo in the primary efficacy parameter, the Children's Depression Rating Scale–Revised (CDRS-R) at Week 8, last observation carried forward (LOCF) analysis.

The sponsor intends to claim long-term treatment effect of escitalopram in adolescents with MDD based on one 24-week double-blind extension study (Study SCT-MD-32A) along with the lead-in study (Study SCT-MD-32). The change from baseline in the lead-in study to the end of Week 24 in CDRS-R score (using the LOCF approach) was proposed by the sponsor as the primary efficacy parameter.

This reviewer evaluated results of Study SCT-MD-32 and Study SCT-MD-32a.

2.2 DATA SOURCES

Data used for review are from the electronic submissions received on May 22, 2008 and December 11, 2008. The network paths are \\CDSESUB1\EVSPROD\NDA021323\0000 , \\CDSESUB1\EVSPROD\NDA021323\00007 , and \\CDSESUB1\EVSPROD\NDA021323\0010

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY SCT-MD-32

3.1.1.1 Objective

The objective of this study was to compare the safety and efficacy of escitalopram relative to placebo at a flexible dose of 10 mg/day or 20 mg/day relative to placebo in the treatment of major depressive disorder in pediatric patients as measured by change from baseline in CDRS-R total score at Week 8.

3.1.1.2 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose (10-20 mg/day) study of the safety and efficacy of escitalopram in the treatment of adolescent patients (12-17 years of age) who have MDD.

As shown in Table 1, the study consisted of a 2-week screening period, including single-blind placebo lead-in during the second week, followed by 8 weeks of double-blind treatment. At the end of the single-blind period, patients meeting the entry criteria for this study were randomized 1:1 to one of two double-blind treatment groups (escitalopram or placebo). The escitalopram dosage was 10 mg/d for the first three weeks of double-blind treatment. The dosage could be increased to 20 mg/d by the investigator at the end of Treatment Week 3 (Visit 6) or Treatment Week 4 (Visit 7). Patients who completed the 8-week double-blind treatment period were eligible to enter a 1-week double-blind down-taper period or to continue in an extension study (Study SCT MD-32A). Patients who prematurely discontinued during Study SCT-MD-32 were also eligible to enter a 1-week double-blind down-taper period.

Table 1. Study SCT-MD-32 Flow Chart

Period	**Screening**		**Double-Blind Treatment**							**Down Taper**
		Single-Blind Placebo	Eslitalopram 10mg/day or Placebo			Eslitalopram 10mg/day, 20mg/day or Placebo				
Visit	1	2	3	4	5	6	7	8	9	10
Study Day/ Week (W)	W -2	W -1	Day 0 / Baseline	W 1	W 2	W 3	W 4	W 6	W 8	W 9

Source: Corresponds to Figure 9.1-1.(pg 24), Clinical Study Report SCT-MD-32.

3.1.1.3 Patient Disposition, Demographic and Baseline Characteristics

This study was conducted at 40 study centers in the United States (US). Of these study centers 38 centers randomized patients. For inclusion in the study, among other criteria, patients had to have CDRS-R score of ≥45 at Visits 1 and 3 and CGI-S score ≥4 at Visit 3.

A total of 584 patients were screened for eligibility; 316 patients were randomized to receive double-blind study drug; 312 patients received at least one dose of double-blind study drug (Safety Population); and 311 patients had at least one postbaseline CDRS-R assessment (ITT Population).

A total of 133 (84.2%) placebo patients and 126 (79.7%) escitalopram patients completed 8 weeks of double-blind treatment, and 202 patients (100 placebo, 102 escitalopram) continued into the extension study, SCT-MD-32A. Of the 57 patients who did not continue into the extension study, 33 (23 placebo, 10 escitalopram) entered the double-blind down-taper period. All of these patients, with the exception of placebo Patient 0163201, completed Study SCT-MD-32 before entering down-taper.

Table 2. Study SCT-MD-32 Patient Population and Disposition

Patients	Escitalopram	Placebo
Randomized	158 (100%)	158 (100%)
Received Study Drug	155 (98.1%)	157 (99.4%)
ITT Population	154 (97.5%)	157 (99.4%)
Discontinued Study	52 (37.1%)	42 (30.0%)
Adverse Event	4 (2.5%)	1 (0.6%)
Lack of therapeutic response	5 (3.2%)	5 (3.2%)
Protocol violation, including lack of compliance	3 (1.9%)	0 (0.0%)
Withdrawal of consent	8 (5.1%)	9 (5.7%)
Lost to Follow-up	8 (5.1%)	6 (3.8%)
Other	1 (0.6%)	3 (1.9%)
Completed study	126 (79.7%)	133 (84.2%)
Enrolled in SCT-MD-32A	102 (64.6%)	100 (63.3%)

Source: Corresponds to Figure 10.1-1.(pg. 51), and Table 10.2-1.(pg. 52) Clinical Study Report SCT-MD-32

The demographic characteristics and the baseline efficacy values of the ITT Population are presented in Table 3 . The average patient age was approximately 15 years, and approximately three quarters of the patients in each treatment group were Caucasian. Females comprised 59% of the Safety Population. There were no statistically significant differences between the two treatment groups with respect to demographic characteristics. The sponsor stated that at baseline there were statistically significant differences in CDRS-R total score and CGI-S between the two treatment groups (at nominal significance level of 0.05), with higher depression severity at baseline in the escitalopram group. The two treatment groups did not have different baseline CGAS scores.

Table 3. Study SCT-MD-32 Demographic and Baseline Characteristics (ITT analysis set)

Variable	Placebo N=157	Escitalopram N=154
Gender, n (%)		
Male	65 (41.4%)	62 (40.3%)
Female	92 (58.6%)	92 (59.7%)
Race		
Caucasian	123 (78.3%)	112 (72.7%)
Black	24 (15.3%)	30 (19.5%)
Asian	0 (0%)	3 (1.9%)
Other	10 (6.4 %)	9 (5.8%)
Age (years)		
Mean (SD)	14.52 (1.48)	14.73 (1.64)
Weight (lbs)		
Mean (SD)	157.4 (47.6)	159.0 (49.8)
Height (in)		
Mean (SD)	65.2 (3.7)	65.1 (3.8)
CDRS-R Total Score		
Mean (SD)	56.0 (8.3)	57.6 (8.3)
CGI-S Total Score		
Mean (SD)	4.4 (0.5)	4.6 (0.6)

Source: Table 14.2.2. (pg. 118), Table 10.3-3. (pg. 54) Clinical Study Report SCT-MD-32.

3.1.1.4 Statistical Methodologies

All efficacy analyses were performed on the ITT Population. All primary and secondary efficacy analyses were performed using the LOCF approach. In this approach, missing postbaseline values were replaced with the last non-missing value before the missing value. Baseline values were not carried forward unless there was at least one non-missing postbaseline visit. The OC approach, in which only observed values are used, was used as a sensitivity analysis. Visit 3 assessments were used as the baseline for all efficacy parameters. All statistical tests were two-sided hypothesis tests performed at 5% level of significance. All confidence intervals were two-sided 95% confidence intervals.

Primary Efficacy Parameter

The primary efficacy parameter was the change from baseline to Week 8 in CDRS-R total score. The primary analysis used the LOCF approach. The between–treatment group comparison was performed using a two-way analysis of covariance (ANCOVA) model with treatment group and study center as factors and the baseline score as a covariate.

A sensitivity analysis for the primary efficacy parameter was performed using the mixed-effects model for repeated measures (MMRM) methodology based on the observed postbaseline longitudinal data. The model included study center, treatment group, visit, and treatment group-by-visit interaction as factors and baseline value as covariate. An unstructured covariance matrix was used for the repeated measures across visits.

Key Secondary Analysis

The key secondary efficacy parameter was the CGI-I score at Week 8. The between–treatment group analysis was performed using an ANCOVA model with treatment group and study center as factors and the baseline CGI-S score as covariate.

3.1.1.5 Results of Efficacy Analysis

Primary Efficacy Analysis

This reviewer confirmed sponsor's primary efficacy analysis. The primary efficacy parameter was the change from baseline to Week 8 in CDRS-R total score. Table 4 presents the results of the ANCOVA analysis for this primary endpoint, using the LOCF approach. The change from baseline to Week 8 in the escitalopram group was clinically and statistically significant and greater than that in the placebo group (LSMD = –3.4, p = .022).

Table 4. CDRS-R Total Score LS Mean Change from Baseline to Week 8 (ITT Population)

		Placebo	Escitalopram
No patients	N=311	157	154
Baseline	Mean (SEM)	56.0 (0.7)	57.6 (0.7)
Change from Baseline	Mean (SEM)	-18.4 (1.1)	-22.4 (1.1)
Placebo-adjusted difference	LS Mean Difference	NA	-3.4
	95% CI	NA	(-6.2, -0.5)
	P-value	NA	0.022

Source: Table 11.1.1.1–1. (pg. 58) Clinical Study Report SCT-MD-32
Remark: SEM stands for Standard Error of the Mean

As seen from Table 5, the observed treatment difference was numerically in favor of escitalopram at Weeks 2, 4, and 6.

Table 5. CDRS-R Total score mean change from baseline by visit with missing values imputed by LOCF method (ITT Population).

	Placebo	Escitalopram	Treatment Difference: Escitalopram - Placebo	
Week	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean**	**95% CI**
2	-11.3 (1.03)	-12.8 (1.00)	-1.48	(-3.83, 0.86)
4	-15.4 (1.06)	-18.8 (1.03)	-3.37	(-5.784, -0.958)
6	-18.6 (1.17)	-21.8 (1.13)	-3.22	(-5.86, -0.57)
8	-18.8 (1.27)	-22.1 (1.22)	-3.36	(-6.23, -0.49)

Source: Table 14.4.3.1A (pg. 162-163) Clinical Study Report SCT-MD-32
Note: The reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

Sensitivity Analysis

The reviewer confirmed sponsor's sensitivity analysis on the primary endpoint. Change from baseline in CDRS-R Total score was analyzed by mixed effect repeated measures model. The model included study center, treatment group, visit, and treatment group-by-visit interaction as factors and baseline CDRS-R total score as covariate. The findings support the primary analysis results.

Table 6. CDRS-R Total Score Change from Baseline Visitwise LS means, Mixed Effects Repeated Measures model (ITT Population).

Week	Study Treatment	Number of patients	LS Mean (SE)	Treatment difference : Escitalopram – Placebo	
				LS Mean (SE)	95 % CI
2	Placebo	145	-12.14 (1.02)		
2	Escitalopram	141	-13.30 (0.99)	-1.16 (1.24)	(-3.61, 1.29)
4	Placebo	144	-16.65 (1.01)		
4	Escitalopram	139	-19.93 (0.98)	-3.28 (1.22)	(-5.69, -0.87)
6	Placebo	135	-19.29(1.09)		
6	Escitalopram	135	-22.53 (1.06)	-3.24 (1.35)	(-5.90, -0.57)
8	Placebo	135	-19.58 (1.16)		
8	Escitalopram	129	-22.71 (1.14)	-3.13 (1.47)	(-6.03, -0.23)

Source: Table 16.1.9.3.1. (pg. 1792-1795), Clinical Study Report SCT-MD-32
Note: The reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

Key Secondary Endpoint

Table 7 presents sponsor's results for the CGI-I score at Week 8, the secondary efficacy endpoint. At Week 8, statistically significant improvement was seen in the escitalopram group relative to the placebo group in the ANCOVA LOCF (LSMD = –0.3, p = .008) analysis with treatment group and study centers as factors and baseline CGI-S score as covariate. This reviewer verified sponsor's results. Whether the magnitude of observed difference is clinically relevant is deferred to the clinical review team.

Table 7. CGI-I Score at Week 8 (ITT Population)

		Placebo	**Escitalopram**
No patients	N=311	157	154
CGI-I at Week 8	Mean (SEM)	2.5 (0.1)	2.2 (0.1)
Placebo-adjusted difference	LS Mean Difference	NA	-0.3
	95% CI	NA	(-0.6, -0.1)
	P-value	NA	0.008

Source: Table 11.1.1.2–1. (pg. 61) Clinical Study Report SCT-MD-32
Remark: SEM stands for Standard Error of the Mean

3.1.1.6 Reviewer's Comments.

Escitalopram treatment group (10mg/d to 20mg/d) was statistically superior to placebo in mean change from baseline to Week 8 in CDRS-R Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with treatment group and study center as factors, and the baseline CDRS-R total score as a covariate was 0.022.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score at Week 8. The p-value of the ANCOVA LOCF analysis was 0.008. Whether the magnitude of the observed treatment difference (LSMD=-0.3) is clinically relevant is deferred to the clinical review team.

3.1.2 STUDY SCT-MD-32A

3.1.2.1 Objective

The objective of this study was to evaluate the **long-term** safety, efficacy, and tolerability of escitalopram at a flexible dose of 10 mg/day or 20 mg/day relative to placebo in the treatment of major depressive disorder in pediatric patients as measured by change from baseline to the endpoint in CDRS-R total score.

3.1.2.2 Study Design

Patients who completed the 8-week double-blind treatment period of Study SCT-MD-32 were eligible to enter the extension study, SCT-MD-32A, for an additional 16-24 weeks of treatment. The final visit of Study SCT-MD-32 double-blind treatment period, Visit 9, was therefore also Visit 1 of Study SCT-MD-32A. Study SCT-MD-32A was initially an open-label extension but

subsequently amended to a double-blind design. Protocol Amendment #2, September 30, 2005, changed the design to a 24-week double-blind extension. Protocol Amendment #3, February 8, 2007, changed the length of the extension to 16 weeks. The study was initiated on June 16, 2005 and completed on September 24, 2007.

During double-blind treatment in Study SCT-MD-32A, patients were to receive the same daily dosage of the blinded study drug they were receiving at Visit 7 of Study SCT-MD-32. The minimum and maximum dosages allowed were 10 mg/d and 20 mg/d. During Study SCT-MD-32A, visits occurred biweekly. Accordingly, patients were given bottles containing 20 tablets of escitalopram 10 mg, escitalopram 20 mg, or matching placebo. Patients who did not enter the extension study entered a 1-week double-blind down-taper period.

Patients who completed the open-label or double-blind treatment period of Study SCT-MD-32A and patients who prematurely discontinued during Study SCT-MD-32A were eligible to enter a 2-week down-taper period, which was open-label or double-blind in correspondence with the patient's treatment group assignment. Patients who prematurely discontinued from Study SCT-MD-32A for insufficient therapeutic response were eligible to receive 6 months of aftercare, provided at the discretion of the investigator.

3.1.2.3 Patient Disposition, Demographic and Baseline Characteristic

As seen from Table 8, of the 259 patients who completed Study SCT-MD-32, 202 enrolled in Study SCT-MD-32A; 165 of these patients were assigned to double-blind escitalopram (N = 83) or placebo (N = 82), and 37 enrolled in the open-label extension. The remaining 57 patients (33 placebo, 24 escitalopram) chose not to continue in the extension study.

Of the 202 patients who entered the extension study (165 double-blind, 37 open-label), approximately 50% (103/202) prematurely discontinued. The most common reason for premature discontinuation during the extension study was insufficient therapeutic response (35 patients [18 placebo, 16 escitalopram, 1 open-label escitalopram]). Overall, 25.3% of patients in the placebo group and 23.4% of patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A. Per the sponsor's study report, more escitalopram-treated patients relative to placebo-treated patients prematurely discontinued during the combined double-blind treatment periods because of AEs (2.5% vs. 0.0%,) and protocol violations (3.8% vs. 1.3%).

Table 8. Study SCT-MD-32/ SCT-MD-32a Patient Population and Disposition

	Escitalopram	Placebo
Patients		
Randomized	158 (100%)	158 (100%)
Received Study Drug	155 (98.1%)	157 (99.4%)
ITT Population	154 (97.5%)	157 (99.4%)
Completed Study SCT-MD-32	126 (79.7%)	133 (84.2%)
Did not continue into Extension	24 (15.2%)	33 (20.9%)
Enrolled in Open Label Extension	19 (12.0%)	18 (11.4%)
Enrolled in Double-Blind (DB) Extension	83 (52.5%)	82 (51.9%)
Discontinued DB Extension	46 (29.1%)	42 (26.6%)
Adverse Event	4 (2.5%)	0 (0%)
Insuffic. therapeutic response	16 (10.1%)	18 (11.4%)
Protocol violation	6 (3.8%)	2 (1.3%)
Withdrawal of consent	10 (6.3%)	8 (5.1%)
Lost to Follow-up	6 (3.8%)	12 (7.6%)
Other	4 (2.5%)	2 (1.3%)
Completed DB Extension	37 (23.4%)	40 (25.3%)

Source: Corresponds to Figure 10.1-1.(pg. 56), and Table 10.2-1.(pg. 58) Clinical Study Report SCT-MD-32a

3.1.2.4 Statistical Methodologies and Endpoints

All efficacy analyses were performed on the combined double-blind treatment periods of Studies SCT-MD-32 and SCT-MD-32A. Baseline for these analyses was defined as the Visit 3 assessment in the lead-in study (SCT-MD-32). All efficacy analyses were performed on the ITT Population.

The change from baseline to the end of study in CDRS-R total score was the primary efficacy parameter. The primary analysis was performed using the LOCF approach. The between-treatment group comparison for the primary efficacy parameter was performed using an analysis of covariance (ANCOVA) model with treatment group and study center as factors and baseline CDRS-R total score as the covariate.

A sensitivity analysis for the primary efficacy parameter was performed using the mixed-effects model for repeated measures (MMRM) methodology based on the observed postbaseline longitudinal data. The model included treatment group, visit, and treatment-group-by-visit interaction as factors and baseline value as covariate. An unstructured covariance matrix was used for the repeated measures across visits.

The secondary efficacy parameter was the CGI-I score at the end of study. The between–treatment group comparison for the secondary efficacy parameter was performed using an ANCOVA model with treatment group and study center as factors and baseline CGI-S score as the covariate.

3.1.2.5 Results of Efficacy Analysis

Primary Efficacy Analysis

The primary efficacy parameter was the change from baseline (Visit 3 of SCT-MD-32) to Week 24 in the CDRS-R total score using the LOCF approach. As shown in Table 9, at the end of the 24-week double-blind treatment period, patients in the escitalopram treatment group had significantly greater improvement relative to placebo-treated patients in the CDRS-R total score using the LOCF approach (least squares mean difference [LSMD] = – 4.5, p = .005). This reviewer confirmed the sponsor's results. However, please see the next section for reviewer's comments.

Table 9. CDRS-R Total Score LS Mean Change from Baseline to Week 24 (ITT population)

		Placebo	**Escitalopram**
No patients	N=311	157	154
Baseline	Mean (SEM)	56.0 (0.7)	56.7 (0.7)
Change from Baseline	Mean (SEM)	-18.2 (1.1)	-23.1 (1.2)
Placebo-adjusted difference	LS Mean Difference	NA	-4.5
	95% CI	NA	(-7.6, -1.3)
	P-value	NA	0.005

Source: Table 11.1.1.1–1. (pg. 66) Clinical Study Report SCT-MD-32a
Remark: SEM stands for Standard Error of the Mean

Key Secondary Endpoint

The secondary efficacy parameter was the CGI-I score at Week 24. At the end of 24 weeks of double-blind treatment, patients receiving escitalopram showed significantly greater improvement relative to placebo-treated patients in the CGI-I score using the LOCF approach (LSMD = – 0.4, p = .003; Table 11.1.1.2–1). These results were confirmed by the reviewer. However, please see the next section for reviewer's comments.

Table 10. CGI-I Score at Week 24 (ITT Population)

		Placebo	**Escitalopram**
No patients	N=311	157	154
CGI-I at Week 24	Mean (SEM)	2.5 (0.1)	2.2 (0.1)
Placebo-adjusted difference	LS Mean Difference	NA	-0.4
	95% CI	NA	(-0.7, -0.1)
	P-value	NA	0.003

Source: Table 11.1.1.2–1. (pg. 69) Clinical Study Report SCT-MD-32a
Remark: SEM stands for Standard Error of the Mean

3.1.2.6 Reviewer's Comments

The primary efficacy endpoint was change from the baseline of Study 32 to the endpoint visit of Study 32a. Note that when the data of acute phase are combined with long-term phase, then the maintenance effect is confounded with acute effect.

Study SCT-MD-32A was initially an open-label extension but subsequently amended to a 24-week double-blind extension, and as the study progressed was further changed to a 16-week double-blind extension. Thus, patients enrolled in the double-blind extension had different exposure times.

Also, the patient population for study 32a consisted of completers of Study 32 who chose to continue into the extension study. Of the 259 patients who completed Study SCT-MD-32, 202 chose to enroll in Study SCT-MD-32A; 165 of these patients continued into the double –blind treatment and received the same blinded study drug they were receiving in Study SCT-MD-32. Thus, treatment groups in Study 32a do not represent random samples of the screened patient population. Typically, to assess maintenance effect patients should be stabilized on the studied medication and then randomized to placebo and drug treatment groups before entering into maintenance phase.

Of the 202 patients who entered the extension study (165 double-blind, 37 open-label), approximately 50% (103/202) prematurely discontinued. The most common reason for premature discontinuation during the extension study was insufficient therapeutic response (35 patients [18 placebo, 16 escitalopram, 1 open-label escitalopram]). Overall, only 25.3% of patients in the placebo group and 23.4% of patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A. For any trial with a very high dropout rate, it is always questionable whether the data can be interpretable.

3.2 EVALUATION OF SAFETY

Background

To assess growth during pediatric depression escitalopram studies, the medical division asked Forest Research Institute to provide analyses of weight (growth) data. Specifically, the medical division asked for analyses that examine changes in mean weight z-scores. For these analyses, the medical division asked the sponsor to assign a z-score to each study subject for baseline and end of study. The z-score is the number of standard deviations from the population mean for a specific subject's weight, given their age and sex. This analysis uses population data from CDC growth charts and allows a determination about whether study subjects are growing along their predicted growth curve. No change in mean z-score would indicate that subjects are growing as predicted by data from age adjusted peers. Decreases in mean z-score would indicate that subjects are lagging behind in growth.

Forest Research Institute responded with a series of tables summarizing the z-score analyses and an electronic data set with weight and z-score data.

Studies reviewed

The weight data analyses submitted by the sponsor came from: one placebo-controlled study with escitalopram in adolescents, 12 to 17 years, (Study SCT-MD-32); one placebo-controlled study with escitalopram (Study CIT-MD-15) in children and adolescents, 7 to 17 years; one placebo-controlled study with citalopram (Study CIT-MD-18) in children and adolescents, 7 to 17 years; and the double-blind extension study (Study SCT-MD-32A).

The three acute treatment controlled trials (Studies 15, 18 and 32) lasted eight weeks. Patients who completed the 8-week double-blind treatment period of Study SCT-MD-32 were eligible to enter the extension study, SCT-MD-32A, for an additional 16-24 weeks of treatment. Study SCT-MD-32A was initially an open-label extension but subsequently amended to a double-blind design.

The acute treatment controlled trials included 282 subjects exposed to escitalopram, 89 patients exposed to citalopram and 373 exposed to placebo. Of the 202 patients enrolled in the extension study, 165 patients entered the double-blind extension (83 escitalopram, 82 placebo), and 37 entered the open-label extension.

Results from individual Randomized Controlled Trials

The sponsor summarized the weight z-scores for individual studies SCT-MD-15, Study SCT-MD-18, and SCT-MD-32. Sponsor's analysis included output tables that provided the mean z-scores at baseline and end of study by treatment. This reviewer confirmed sponsor's results and conducted exploratory descriptive subgroup analysis by age (children, adolescents), and gender. See Tables 11, 12 and 13 below for details. In all three studies, for all treatment arms the mean change in z-score was in the range from 0.2 to 0.5, except the citalopram arm in study SCT-MD-18. The difference between the treatment arms in Study SCT-MD-18 appeared to be mainly driven by the female subgroup.

Table 11. Mean change from baseline in weight z-scores for Study 15.

Study 15	**Placebo**		**Escitalopram**	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Overall	132		129	
Baseline		1.25 (0.99)		1.06 (1.11)
Change		0.05 (0.13)		0.04 (0.13)
Children	52		52	
Baseline		1.46 (0.91)		1.08 (1.16)
Change		0.05 (0.14)		0.07 (0.13)
Adolescents	80		77	
Baseline		1.11 (1.02)		1.04 (1.08)
Change		0.05 (0.12)		0.02 (0.13)
Male	63		63	
Baseline		1.12 (0.92)		0.77 (1.14)
Change		0.06 (0.14)		0.05 (0.13)
Female	69		66	
Baseline		1.37 (1.05)		1.33 (1.01)
Change		0.04 (0.11)		0.03 (0.13)

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Table 12. Mean change from baseline in weight z-scores for Study18

Study 18	Placebo		Citalopram	
	N	Mean (SD)	N	Mean (SD)
Overall	85		89	
Baseline		1.07 (1.20)		1.11 (1.25)
Change		0.04 (0.13)		0.00 (0.17)
Children	38		45	
Baseline		1.16 (1.27)		1. 31 (1.28)
Change		0.06 (0.15)		0.01 (0.16)
Adolescents	47		44	
Baseline		0.99 (1.14)		0.92 (1.20)
Change		0.03 (0.10)		-0.02 (0.18)
Male	39		42	
Baseline		0.95 (1.21)		1.13 (1.28)
Change		0.04 (0.13)		0.03 (0.19)
Female	46		47	
Baseline		1.16 (1.19)		1.10 (1.23)
Change		0.05 (0.12)		-0.04 (0.15)

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Table 13. Mean change from baseline in weight z-scores for Study 32.

Study 32	Placebo		Escitalopram	
	N	Mean (SD)	N	Mean (SD)
Overall	156		153	
Baseline		1.24 (1.11)		1.20 (1.17)
Change		0.04 (0.12)		0.02 (0.13)
Male	64		61	
Baseline		1.33 (1.25)		1.33 (1.25)
Change		0.06 (0.14)		0.04 (0.12)
Female	92		92	
Baseline		1.17 (1.00)		1.12 (1.12)
Change		0.02 (0.10)		0.01 (0.13)

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Results from Pooled Data

Per medical officer's request, the sponsor pooled the escitalopram/citalopram exposure data from the randomized controlled trials (studies 15, 18, and 32) to calculate mean changes in z-score. This reviewer confirmed the sponsor's results and conducted additional exploratory descriptive subgroup analysis by gender (see Table 14). Numerically, the results appeared to be consistent among the treatment groups, except the female subgroup randomized to citalopram arm. For citalopram female subgroup the mean change in weight z-score was -0.04. For all other subgroups the mean change in z-score was in the range from 0.2 to 0.5.

Table 14. Pooled analysis: Mean change from baseline in weight z-scores.

Pooled	Placebo		Citalopram		Escitalopram	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Overall	373		89		282	
Baseline		1.20 (1.09)		1.11 (1.25)		1.13 (1.14)
Change		0.04 (0.125)		0.00 (0.17)		0.03 (0.129)
Male	166		42		124	
Baseline		1.16 (1.13)		1.13 (1.28)		1.04 (1.22)
Change		0.05 (0.14)		0.03 (0.19)		0.04 (0.13)
Female	207		47		158	
Baseline		1.23 (1.06)		1.10 (1.23)		1.21 (1.07)
Change		0.04 (0.11)		-0.04 (0.15)		0.02 (0.13)

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Results from Extension Study

Using the submitted electronic data sets, this reviewer conducted additional exploratory descriptive analysis of the weight z-scores using only the data for those subjects who continued into the extension treatment (Study SCT-MD-32A). For patients who participated in the double-blind extension, the mean z-score changes were numerically consistent between the treatment groups: change in mean z-score of 0.09 for escitalopram group and 0.08 for placebo group. The results were also consistent within gender subgroups and by visit (see Tables 15 and 16). This reviewer noticed that there were unusual fluctuations in the numbers of patients having z-score assessments after Week 12. This reviewer further determined that all patients with z-score assessments at Week 16 did not have any assessments at Week 14 or Week 18. One possible explanation of the fluctuations could be that some patients were scheduled for visits at different study weeks. Thus, the numerical results presented in Table 16 should be interpreted with caution.

For the open-label extension, the escitalopram/escitalopram subjects experienced an increase in mean z-score of 0.04 from the beginning of the double-blind phase. The subjects who received escitalopram for the first time during the open label phase experienced a mean decrease in z-score of -0.01 (see Table 15).

Table 15. Mean change from baseline in weight z-scores for Study 32/32A

Study 32/32A	Placebo		Escitalopram	
	N	Mean (SD)	N	Mean (SD)
Overall	82		83	
Baseline		1.37 (1.17)		1.10 (1.20)
Change		0.08 (0.15)		0.09 (0.21)
Male	38		31	
Baseline		1.42 (1.35)		1.52 (1.40)
Change		0.10 (0.18)		0.13 (0.17)
Female	44		52	
Baseline		1.34 (0.99)		0.84 (0.99)
Change		0.06 (0.11)		0.06 (0.23)
	Placebo+Open Label Escitalopram		**Escitalopram+Open Label Escitalopram**	
Baseline	18	1.02 (0.95)	19	1.54 (1.26)
Change	18	-0.01 (0.11)	19	0.04 (0.14)

Source: Sponsor's submission \\CDSESUB1\EVSPROD\NDA021323\00007 and reviewer's results

Table 16. Study 32/32A. Mean change from baseline in weight z-scores by week.

Study 32/32A	Placebo		Escitalopram	
	N	Mean (SD)	N	Mean (SD)
Baseline	82	1.37 (1.17)	83	1.10 (1.20)
Week 1	80	-0.00 (0.06)	76	-0.01 (0.07)
Week 2	76	0.01 (0.07)	78	-0.01 (0.07)
Week 3	77	0.02 (0.09)	77	-0.02 (0.07)
Week 4	81	0.04 (0.08)	80	-0.01 (0.09)
Week 6	76	0.04 (0.09)	80	-0.01 (0.13)
Week 8	81	0.04 (0.12)	82	0.02 (0.12)
Week 10	72	0.05 (0.11)	72	0.04 (0.16)
Week 12	64	0.06 (0.11)	65	0.07 (0.18)
Week 14	13	0.04 (0.08)	18	0.04 (0.19)
Week 16	48	0.07 (0.13)	48	0.10 (0.17)
Week 18	8	0.04 (0.07)	4	0.06 (0.15)
Week 20	40	0.05 (0.15)	39	0.11 (0.21)
Week 22	10	0.04 (0.17)	8	0.10 (0.13)
Week 24	40	0.09 (0.17)	39	0.13 (0.24)

Source: Reviewer's Results

Statistical Comment

Numerically, the weight z-score changes appeared to be similar between the treatment groups for all studies.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

4.1.1 STUDY 32

This reviewer conducted exploratory subgroup analysis on the primary efficacy variable (change from baseline in CDRS-R Total score at week 8), using ANCOVA models, including the terms for treatment and the baseline score. The subgroups of interest included gender and race. For all subgroups except the black race the treatment effect appeared to be numerically in favor of escitalopram when compared with placebo.

Table 17. Subgroup Analysis: CDRS-RS Total score mean change from baseline with missing values imputed by LOCF method.

Subgroup	Placebo		Escitalopram		Treatment Difference: Escitalopram - Placebo	
	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean (SE)	95% CI
Gender						
Male	65	-18.75 (1.70)	62	-21.84 (1.74)	-3.09 (2.45)	(-7.93, 1.75)
Female	92	-18.81 (1.36)	92	-22.25 (1.36)	-3.44 (1.93)	(-7.24, 0.37)
Race						
White	123	-17.90 (1.19)	112	-22.73 (1.25)	-4.83 ((1.72)	(-8.23, -1.43)
Black	24	-24.74 (2.39)	30	-18.38 (2.13)	6.36 (3.26)	(-0.17, 12.90)
Other	10	-18.22 (5.29)	12	-22.90 (4.83)	-4.67 (7.17)	(-19.67, 10.32)

Source: Reviewer's Results
Note: the reported 95% CIs are nominal and are not adjusted for multiplicity.

4.1.2 STUDY 32A

Omitted, because the results on the overall population are not interpretable.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Not available.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Study SCT-MD-32

Escitalopram treatment group (10mg/d to 20mg/d) was statistically superior to placebo in mean change from baseline to Week 8 in CDRS-R Total score. The p-value of pairwise comparison with placebo obtained from LOCF ANCOVA model with treatment group and study center as factors, and the baseline CDRS-R total score as a covariate was 0.022.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score at Week 8. The p-value of the ANCOVA LOCF analysis was 0.008. Whether the magnitude of the observed treatment difference (LSMD=-0.3) is clinically relevant is deferred to the clinical review team.

No statistical issues were found.

Study SCT-MD-32a

The primary efficacy endpoint was change from the baseline of Study 32 to the endpoint visit of Study 32a. Note that when the data of acute phase are combined with long-term phase, then the maintenance effect is confounded with acute effect.

Study SCT-MD-32A was initially an open-label extension but subsequently amended to a 24-week double-blind extension, and as the study progressed was further changed to a 16-week double-blind extension. Thus, patients enrolled in the double-blind extension had different exposure times.

Also, the patient population for study 32a consisted of completers of Study 32 who chose to continue into the extension study. Of the 259 patients who completed Study SCT-MD-32, 202 chose to enroll in Study SCT-MD-32A; 165 of these patients continued into the double –blind treatment and received the same blinded study drug they were receiving in Study SCT-MD-32. Thus, treatment groups in Study 32a do not represent random samples of the screened patient population. Typically, to assess maintenance effect patients should be stabilized on the studied medication and then randomized to placebo and drug treatment groups before entering into maintenance phase.

Of the 202 patients who entered the extension study (165 double-blind, 37 open-label), approximately 50% (103/202) prematurely discontinued. The most common reason for premature discontinuation during the extension study was insufficient therapeutic response (35 patients [18 placebo, 16 escitalopram, 1 open-label escitalopram]). Overall, only 25.3% of patients in the placebo group and 23.4% of patients in the double-blind escitalopram group completed both studies SCT-MD-32 and SCT-MD-32A. For any trial with a very high dropout rate, it is always questionable whether the data can be interpretable.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Study SCD-MD-32

In the primary analysis of CDRS-R Total score, adolescent patients (12-17 years of age) with Major Depressive Disorder on escitalopram 10-20mg/d were observed to show statistically significant improvement over patients in the placebo treatment group.

Escitalopram group also showed statistically significant improvement relative to placebo in the CGI-I score. Whether the magnitude of the observed treatment difference is clinically relevant is deferred to the clinical review team.

Study SCD-MD-32a

In this reviewer's opinion, this trial does not provide interpretable evidence for the long-term efficacy (maintenance) claim.

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/s/

George Kordzakhia
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Peiling Yang
1/28/2009 12:48:30 PM
BIOMETRICS

James Hung
1/28/2009 07:06:05 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Escitalopram Oxalate-Lexapro
PRIMARY REVIEWER: Andre Jackson
TYPE: SNDA
NDA: 21323/S-30/S30-Tablets
STRENGTH: 5 mg, 10 mg and 20 mg
NDA: 21365/S-20/S21-Oral Solution
STRENGTH: 5 mg/5ml

APPLICANT: Forest Laboratories
Submission Date:
May 22, 2008

INDICATIONS: Depression

Review of Three Pharmacokinetic studies in Adolescent Children 12-17 Years for Lexapro

TABLE OF CONTENTS

STUDY CIT-PK-07 COMPARISON OF CITALOPRAM PHARMACOKINETICS IN ADULTS AND PEDIATRICS FOLLOWING A 40 MG DOSE

INTRODUCTION

Citalopram (CIT) is a bicyclic phthalein derivative which pharmacologically is characterized as a selective and potent inhibitor of the neuronal uptake of serotonin (5-HT) in the central nervous system. Escitalopram, the pure S-enantiomer of CIT, is primarily responsible for the serotonin reuptake inhibition produced by CIT. The bioavailability of citalopram is nearly complete with negligible first-pass metabolism. The predominant metabolite of CIT in humans is demethylcitalopram (DCT). Compared to CIT, this metabolite is present in lower concentrations and is relatively inactive as a serotonin reuptake inhibitor (SRI). The half-lives of CIT and DCT in normal healthy volunteers are approximately 35 and 60 hours, respectively. Another less predominant metabolite,

didemethylcitalopram (DDCT), has a half-life of 100 hours and is even less active than DCT as an SRI. Elimination of citalopram is predominantly hepatic (87%).

PURPOSE OF THE STUDY

The primary objective of this study was to evaluate the pharmacokinetics of citalopram, DCT (demethylcitalopram), and DDCT (didemethylcitalopram) and their enantiomers in pediatric patients with depression (compared to adult patients with depression), following titration to a dose of 40 mg daily from a starting dose of 20 mg daily. The secondary objectives were to assess the safety and efficacy of citalopram in pediatric patients.

Since the S-enantiomer of CIT is responsible for activity only R-citalopram, S-citalopram, S-demethyl-citalopram and S-didemethylcitalopram will be reported in this review.

METHODS

The study was a 4 week, open-label, parallel groups, multiple-dose, dose-escalating study. The study was done in a single group of pediatric patients from 10-17 years of age for comparison with the adult patients 21-45 yrs of age.

The patients received racemic citalopram at a starting dose of 20 mg daily for one week and then received citalopram 40 mg daily for 3 weeks.

Blood and urine samples for pharmacokinetic analysis were collected throughout the study.

Demographics:

	Adult N=12	Pediatric N=13	All Patients N=25
Age, years			
Mean	36	14.2	24.7
Standard Deviation	6.4	1.9	12.0
Min – Max	21, 44	10, 17	10, 44
Weight, kg			
Mean	77.6	62.3	69.6
Standard Deviation	14.95	11.69	15.2
Min – Max	55.8, 102.5	41.2, 78.2	41.2, 102.5
Height, cm			
Mean	172.8	165.9	169.2
Standard Deviation	12.3	12.8	12.8
Min – Max	157.0, 193.0	146.0, 191.7	146.0, 193.0

Twenty-three (23) of the 25 patients who were enrolled completed the study. Two patients #01131, 16 years old (unable to establish reliable venous access on Day 1) and #02105, an adult (lost to follow-up on Day 20) did not complete the study.

Blood Sampling and Collection Procedure

Twenty-four (24) blood samples for determination of the concentrations of the enantiomers of citalopram and their metabolites were collected. Seventeen (17) blood samples for determination of the concentration of the enantiomers of citalopram and their metabolites were collected for the patient under 12 years of age.

Day 1: 0.0 hour (pre-dose) and 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0 hours post-dose
Day 2: 24.0 hours (post-dose)
Day 8: 0.0 hour (pre-dose)
Day 27: 0.0 hour (pre-dose)
Day 28: 0.0 hour (pre-dose), and 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 hours postdose.
Days 29, 30, 32, 34, and 35: 24.0, 48.0, 96.0, 144.0, and 168.0 hours post the Day 28 final drug dose.

For the patient under 12 years of age only 17 blood samples were collected, for a total of 145 mL of blood (including 60 mL for pre-study, Day 8, and post-study clinical analysis), at the following timepoints:
Day 1: 0.0 hour (pre-dose) and 1.0, 2.0, 4.0, 8.0, and 12.0 hours post-dose
Day 2: 24 hours post dose

Day 8: 0.0 hour (pre-dose)
Day 28: 0.0 hour (pre-dose), and 1.0, 2.0, 4.0, 8.0, and 12.0 hours post-dose.
Days 29, 30, and 32: 24.0, 48.0, and 96.0, hours post the Day 28 final drug dose.

DATA ANALYSIS

The area under the plasma concentration time curve (AUC0-t and AUC0-∞), maximum plasma concentration (Cmax), time of maximum plasma concentration (Tmax), and elimination half-life (t½) were obtained from the plasma concentrations as described below. The areas under the plasma concentration versus time curves up to the last measurable concentration (AUC0-t) were estimated by numerical integration using the linear trapezoidal rule

$$AUC_{0-t} = \sum_{i=2}^{n} 0.5 \ (C_i + C_{i-1}) \ (t_i - t_{i-1})$$

where Ci was the plasma concentration at the corresponding sampling time point ti. The values of the elimination rate constant (λz) for citalopram, DCT, R-CT, escitalopram, R-DCT and S-DCT were determined by a non-compartmental analysis. A regression analysis was performed on the terminal linear phase of the semi-logarithmic plots of individual plasma concentration time-data.

STATISTICAL EVALUATION

Pharmacokinetic Parameters
Estimates of mean values obtained for pharmacokinetic parameters were compared between age groups and between genders using standard statistical procedures. Statistical analyses were performed with the Statistical Analyses System (SAS) version 6.12 for the UNIX system microcomputer using the General Linear Models procedure (GLM).
Analysis of variance (ANOVA) was performed on the pharmacokinetic parameters including Cmax, AUC0-24 and Tmax after the initial doses, and Cmax, AUCss, Tmax, t½, Vz/F, CL/F and Ae0-24 after the final dose. AUC and Cmax were log-transformed in the analysis of variance.

Analytical
DETAILED STUDY REPORTS
ASSAY VALIDATION
Analytical- The assay for citalopram was a chiral assay.

Parameter	R-citalopram	S-citalopram	S-demethyl-citalopram	S-didemethylcitalopram
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Concentration Range	3.75-75 ng/ml	3.75-75 ng/ml	3.75-75 ng/ml	3.75-75 ng/ml
Number of Freeze-thaw	3	3	3	3
Benchtop Stability at RT	2 hrs	2 hrs	2 hrs	2 hrs
Long term at –30° C	27 months	27 months	27 months	27 months
Extraction Recovery	(b) (4)			

WITHIN STUDY RESULTS:
Study Dates: August 9, 1999 to November 11, 2000
Total Storage: 15 months

Parameter	R-Citalopram	S-Citalopram	S-demethyl-citalopram	S-didemethylcitalopram
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ	1 ng/ml	1 ng/ml	1 ng/ml	1 ng/ml
Linearity (Standard curve samples)	1-150 ng/ml	1-150 ng/ml	1-150 ng/ml	1-150 ng/ml
Quality Control (QC) Samples	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml
Precision of Standards (%CV)	1.8% @ 1 ng/ml 2.5% @ 150	1.7% @ 1 ng/ml 2.4% @ 150	4.2% @ 1 ng/ml 2.0% @ 150	1.9% @ 1 ng/ml 2.7% @ 150

	ng/ml	ng/ml	ng/ml	ng/ml
Precision of QC Samples (%CV)	5.7% @3.75 ng/ml 6.3% @ 75 ng/ml	7.9% @3.75 ng/ml 7.3% @ 75 ng/ml	7.7% @3.75 ng/ml 8.2% @ 75 ng/ml	6.3% @3.90 ng/ml 7.0% @ 78 ng/ml
Accuracy of Standards (%)	99% @ 1 ng/ml 99% @ 150 ng/ml	99.4% @ 1 ng/ml 99.7% @ 150 ng/ml	99% @ 1 ng/ml 99% @ 150 ng/ml	99% @ 1 ng/ml 99% @ 150 ng/ml
Accuracy of QC Samples (%)	98% @ 1 ng/ml 99% @ 75 ng/ml	96% @ 1 ng/ml 99% @ 75 ng/ml	97% @ 1 ng/ml 97% @ 75 ng/ml	96.5@3.9 ng/ml 98%@78 ng/ml

RESULTS

Table 1. Incidence of Treatment Emergent Adverse Events (≥3 patients)

Best possible copy

Preferred Term	Adult (N=12) n (%)	Pediatric (N=13) n (%)
Patients with at least one TEAE	12 (100)	10 (76.9)
Headache	5 (41.7)	3 (23.1)
Nausea	2 (16.7)	3 (23.1)
Fatigue	1 (8.3)	3 (23.1)
Rhinitis	3 (25.0)	1 (7.7)
Decreased Appetite	1 (8.3)	2 (15.4)
Dry Mouth	2 (16.7)	1 (7.7)
Insomnia	1(8.3)	2 (15.4)
Lightheaded feeling	3 (25)	0 (0)

The adverse events appeared to be comparable in adults and pediatric populations.

PHARMACOKINETIC RESULTS

In general, none of the patients had detectable concentrations of didemethylcitalopram during the 24 hour period after the initial dose of 20 mg citalopram and the concentrations for didemethylcitalopram in the steady state were too low to estimate the pharmacokinetic parameters. Therefore, the pharmacokinetic parameters for didemethylcitalopram were not calculated.

The PDR reports, " At steady state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin

reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram. In addition 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. For this review results for S and R citalopram will be presented.

Pharmacokinetics

SINGLE DOSING

Figure 1. Plasma Concentrations (mean±SD) of Escitalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric vs. Adult Patients

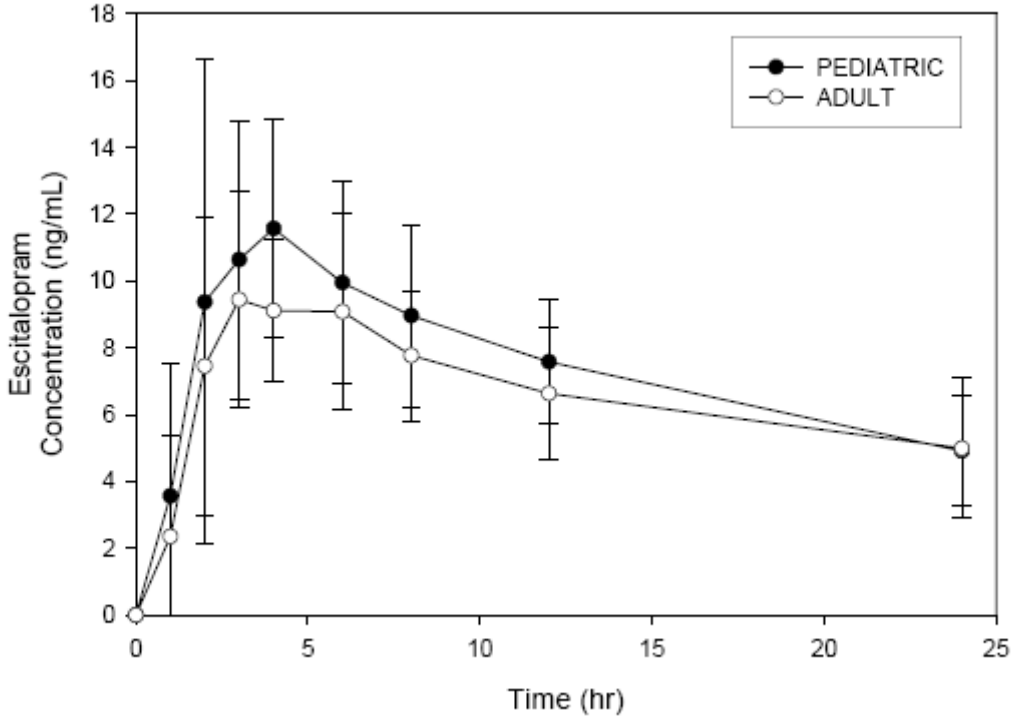


Figure 2. Plasma Concentrations (mean±SD) of R-citalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric vs. Adult Patients.

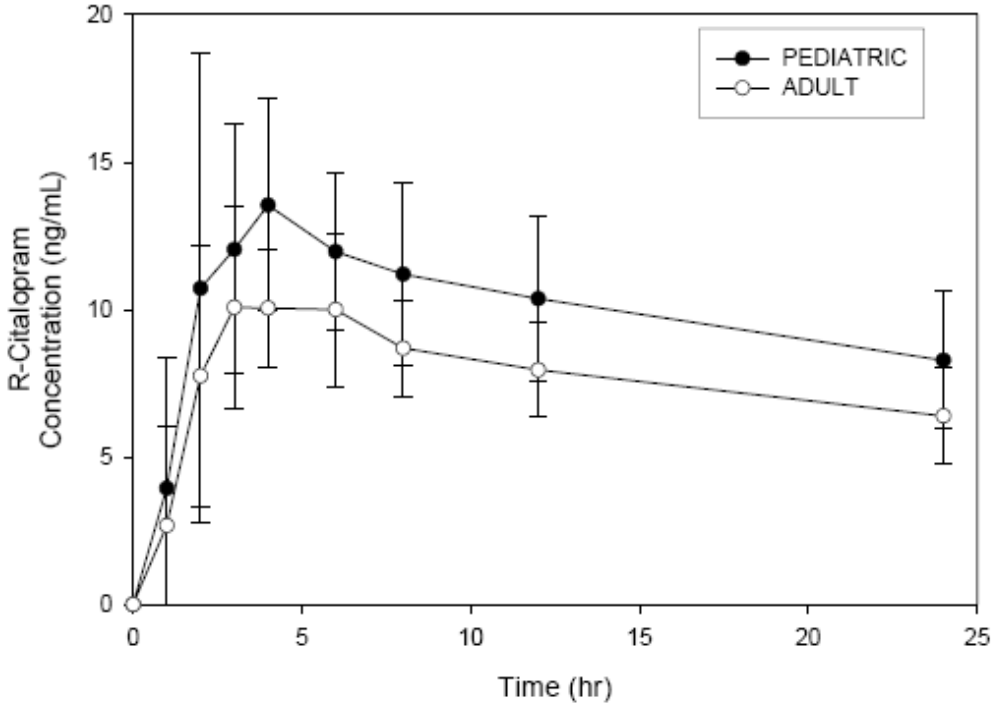


Figure 3. Plasma Concentrations (mean±SD) of Escitalopram after a Single Dose Administration of 20 mg Citalopram in Male vs. Female Patients.

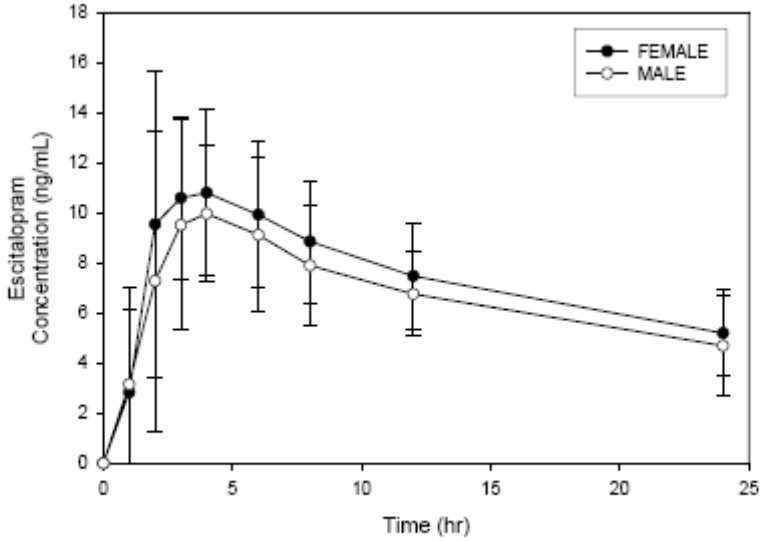


Figure 4. Plasma Concentrations (mean±SD) of R-citalopram after a Single Dose Administration of 20 mg Citalopram in Male vs. Female Patients.

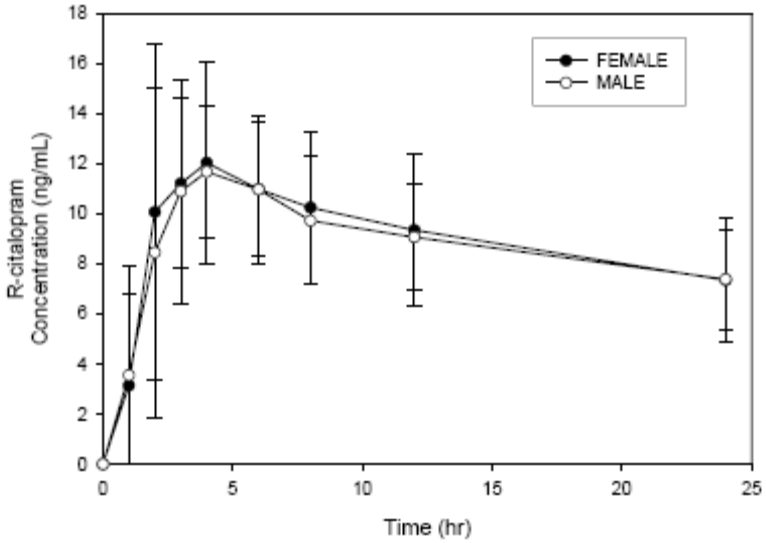


Table 1. Pharmacokinetic Parameters (Mean ± SD) Escitalopram following a Single Dose of 20 mg Citalopram in Adult and Pediatric Patients.

Escitalopram			
PK Parameters	Adult (N=11)	Pediatric (N=12)	p-value
C_{max} (ng/mL)	11.2 ± 2.8	13.1 ± 4.4	0.149
T_{max} (hr)	3.4 ± 1.8	3.5 ± 1.4	0.809
AUC_{0-24} (hr* ng/mL)	157.4 ± 41.2	179.4 ± 52.2	0.196

Table 2. Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following a Single Dose of 20 mg Citalopram in Female and Male Adult and Pediatric Patients.

Escitalopram			
PK Parameters	Female (N=12)	Male (N=11)	p-value
C_{max} (ng/mL)	12.9 ± 3.6	11.4 ± 4.0	0.168
T_{max} (hr)	3.5 ± 1.6	3.3 ± 1.6	0.809
AUC_{0-24}(hr* ng/mL)	178.0 ± 49.5	158.9 ± 45.6	0.232

MULTIPLE DOSING

Figure 5. Plasma Concentrations (mean±SD) of Escitalopram after a Multiple Dose Administration of 40 mg/day Citalopram in Pediatric vs. Adult Patients.

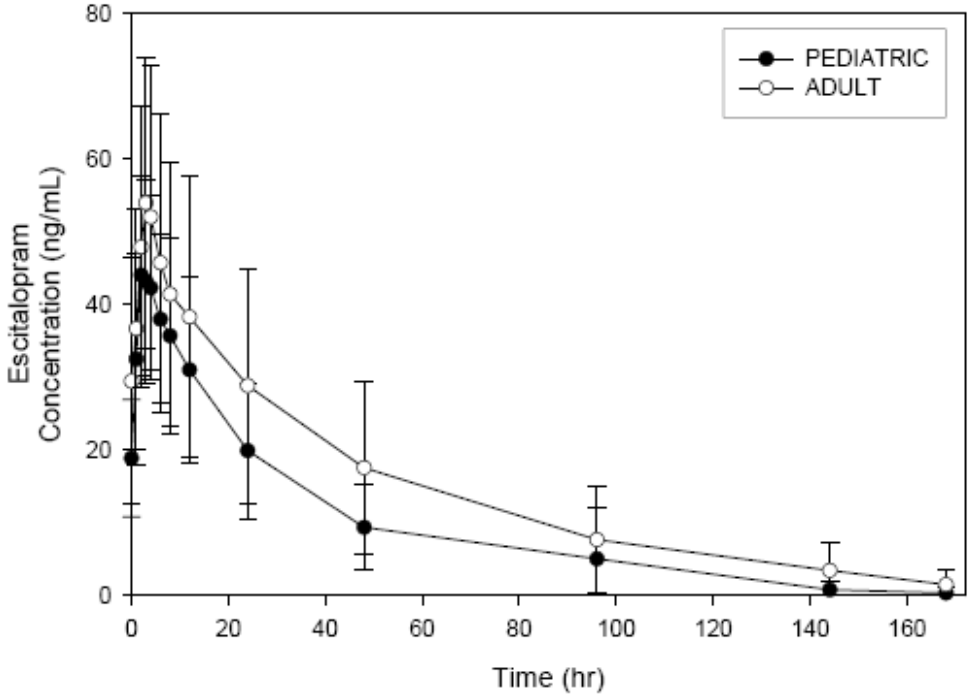


Figure 6. Plasma Concentrations (mean±SD) of R-citalopram after a Multiple Dose Administration of 40 mg/day Citalopram in Pediatric vs. Adult Patients.

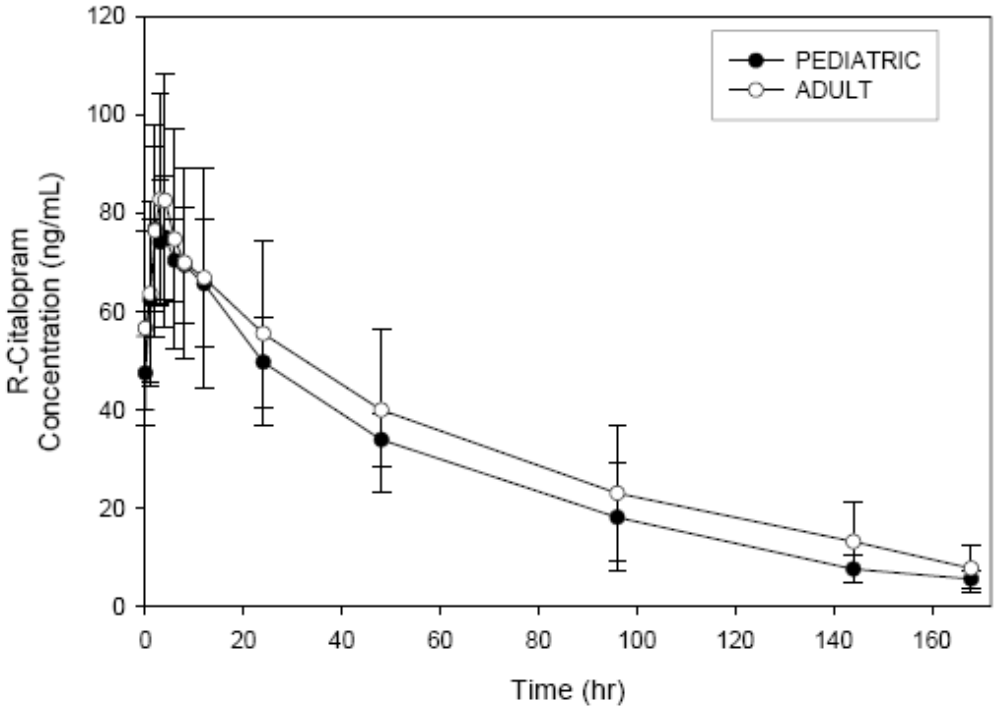


Table 3. Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following Multiple Dose Administration of 40 mg/day Citalopram in Adult and Pediatric Patients

Escitalopram			
PK Parameters	Adult (N=11)	Pediatric (N=12)	p-value
C_{max} (ng/mL)	57.2 ∀ 21.2	47.1 ± 13.9	0.327
T_{max} (hr)	2.8 ± 0.6	2.6 ± 1.3	0.524
AUC_{ss} (hr* ng/mL)	935.7 ± 434.9	745.2 ± 270.8	0.447
$t_{1/2}$ (hr)	31.4 ± 9.8	27.9 ± 12.6	0.524
CL/F (L/hr)	52.9 ± 24.1	60.2 ± 21.5	0.622
Vz/F (L)	2151.9 ± 707.8	2465.4 ± 1672.5	0.687
Ae_{0-24} (mg)	3.5[a] ± 2.4	2.3[a] ± 1.3	0.190

Table 4. Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following Multiple Dose Administration of 40 mg/day Citalopram in Female and Male Patients.

Escitalopram			
PK Parameters	Female (N=12)	Male (N=11)	p-value
C_{max} (ng/mL)	54.1 ± 15.7	49.6 ± 20.9	0.578
T_{max} (hr)	2.8 ± 0.8	2.6 ± 1.3	0.887
AUC_{ss}(hr* ng/mL)	880.3 ± 312.5	778.3 ± 418.5	0.432
$t_{1/2}$ (hr)	30.5 ± 11.9	28.5 ± 11.0	0.807
CL/F (L/hr)	51.0 ± 18.1	62.9 ± 26.0	0.278
Vz/F (L)	2111.1 ± 826.1	2538.4 ± 667.0	0.514
Ae_{0-24} (mg)	3.0[a] ± 1.8	2.9[a] ± 2.2	0.864

Table 5. Individual and Mean Pharmacokinetic Parameters of R-citalopram after Administration of a Single dose of 20 mg and Multiple Daily Dose of 40 mg/day Citalopram.

				Single Dose			Multiple Dose						
AGE	SUBJECT	SITE	SEX	T_{max} hour	C_{max} ng/mL	AUC_{0-24} hr*ng/mL	Ae_{0-24} mg	C_{max} ng/mL	T_{max} hour	$t_{1/2}$ hour	AUC_{ss} hr*ng/mL	Vz/F L	CLss/F L/hr
Pediatric	26	1	M	2.0	15.3	261.6	8.2	84.7	1.0	43.1	1418.5	1751.7	28.2
Pediatric	26	2	M	4.0	13.2	248.0	5.3	61.2	4.0	65.8	1038.7	3657.2	38.5
Pediatric	27	2	M	2.0	11.3	175.0	4.6	72.5	1.0	43.9	1350.1	1877.1	29.6
Pediatric	28	1	M	4.0	11.5	189.6	3.3	66.4	3.0	35.6	1372.8	1497.3	29.1
Pediatric	28	2	M	4.0	11.2	168.4	NA	73.9	6.0	49.4	1563.7	1824.2	25.6
Pediatric	29	1	M	2.0	22.5	328.0	5.2	106.5	2.0	40.6	1974.5	1186.4	20.3
Pediatric	29	2	F	4.0	11.2	170.8	3.6	77.6	1.0	39.5	1537.6	1482.5	26.0
Pediatric	30	1	M	4.0	12.5	196.6	4.9	70.3	6.0	38.0	1371.2	1599.5	29.2
Pediatric	30	2	F	3.0	15.9	256.1	NA	68.8	4.0	62.3	1487.3	2416.5	26.9
Pediatric	31	2	F	6.0	15.4	244.7	6.1	91.0	3.0	33.0	1553.8	1224.4	25.7
Pediatric	32	1	F	6.0	14.7	233.4	7.1	84.2	8.0	42.4	1754.4	1395.1	22.8
Pediatric	S1(Child)	1	F	2.0	24.3	401.9	5.5	111.4	2.0	33.5	1913.1	1010.4	20.9
			Mean	3.6	14.9	239.5	5.4	80.7	3.4	43.9	1528.0	1743.5	26.9
			SD	1.4	4.4	69.7	1.5	15.7	2.3	10.5	258.4	708.9	4.8
			Min	2.0	11.2	168.4	3.3	61.2	1.0	33.0	1038.7	1010.4	20.3
			Max	6.0	24.3	401.9	8.2	111.4	8.0	65.8	1974.5	3657.2	38.5
			CV%	40.3	29.2	29.1	27.7	19.4	66.6	23.9	16.9	40.7	17.9

NA: Not Available

ADDENDUM TO STUDY CIT-PK-07-EXCLUSION OF 10 YR OLD SUBJECT

The label for study CIT-PK-07 states an age range of 12-17; however, the study was done in subjects 10-17. To be consistent with the label a female subject age 10 was removed from the data set and the analysis repeated.

Single Dosing

Figure 1. Plasma Concentrations (Mean ± SD) of Escitalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric (excluding 10 year-old female patient) vs. Adult Patients

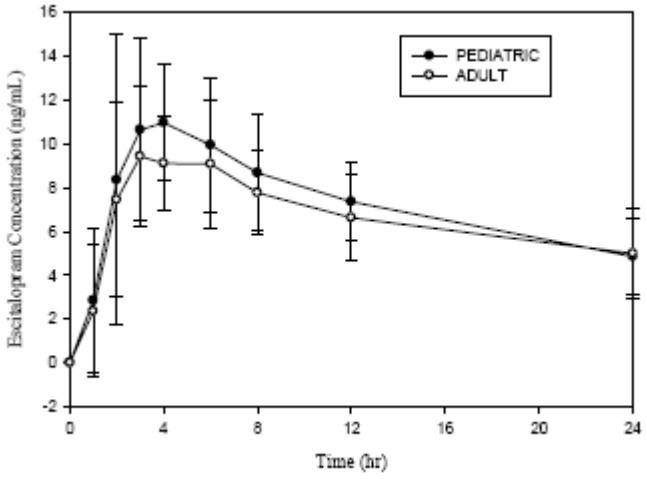


Figure 2. Plasma Concentrations (Mean ± SD) of R-citalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric (excluding 10 year-old female patient) vs. Adult Patients

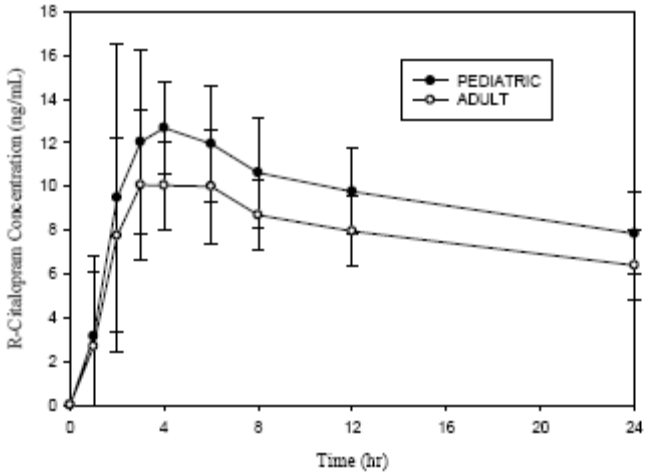


Figure 3. Plasma Concentrations (Mean ± SD) of Escitalopram after a Single Dose Administration of 20 mg Citalopram in Male vs. Female (excluding 10 year-old female) Patients

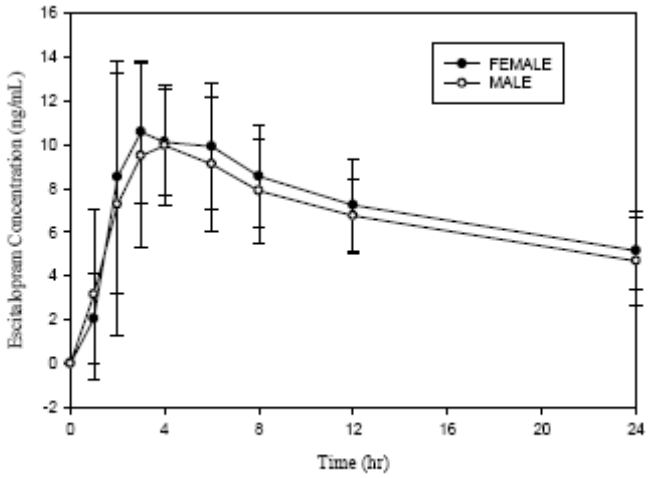


Figure 4. Plasma Concentrations (Mean ± SD) of R-Citalopram after a Single Dose Administration of 20 mg Citalopram in Male vs. Female (excluding 10 year-old female) Patients

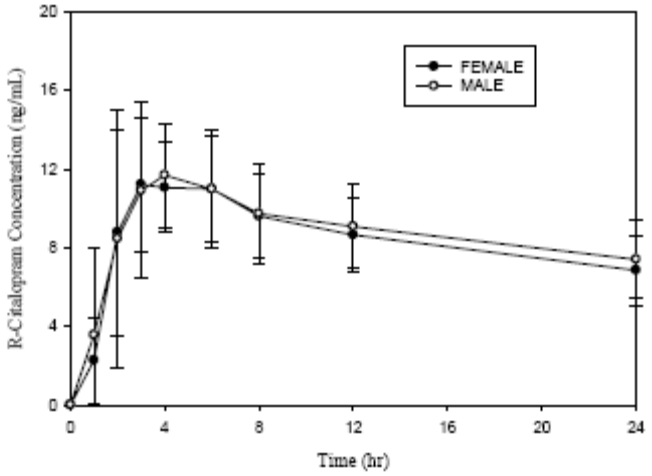


Table 1.	Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following a Single Dose of 20 mg Citalopram in Adult and Pediatric Patients (excluding 10 year-old female patient)		
	Escitalopram		
PK Parameters	Adult (N = 11)	Pediatric (N = 11)	p value
C_{max} (ng/mL)	11.2 ± 2.8	12.4 ± 3.9	0.622
T_{max} (hr)	3.4 ± 1.8	3.6 ± 1.4	0.521
AUC_{0-24} (ng•h/mL)	157.4 ± 41.2	172.2 ± 48.1	0.431

Table 2.	Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following a Single Dose of 20 mg Citalopram in Female and Male Adult and Pediatric Patients (excluding 10 year-old female patient)		
	Escitalopram		
PK Parameters	Female (N = 11)	Male (N = 11)	p value
C_{max} (ng/mL)	12.2 ± 2.7	11.4 ± 4.0	0.264
T_{max} (hr)	3.6 ± 1.6	3.3 ± 1.6	0.787
AUC_{0-24} (ng•h/mL)	170.7 ± 44.6	158.9 ± 45.6	0.599

Multiple Dosing

Figure 5. Plasma Concentrations (Mean ± SD) of Escitalopram after Multiple-Dose Administration of 40 mg Citalopram in Pediatric (excluding 10 year-old female patient) vs. Adult Patients

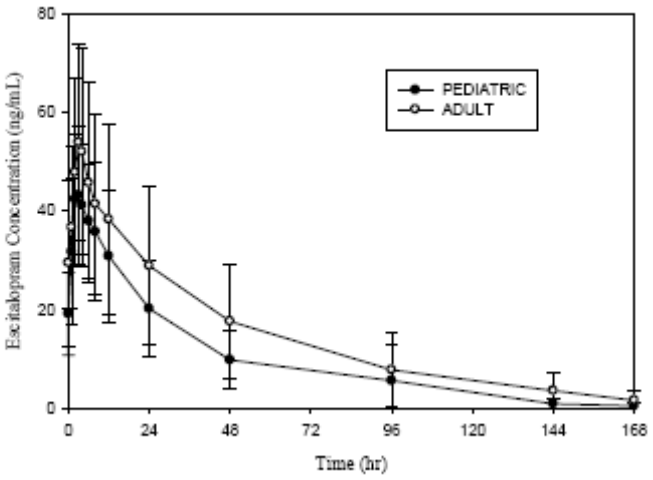


Figure 6. Plasma Concentrations (Mean ± SD) of R-citalopram after Multiple-Dose Administration of 40 mg Citalopram in Pediatric (excluding 10 year-old female patient) vs. Adult Patients

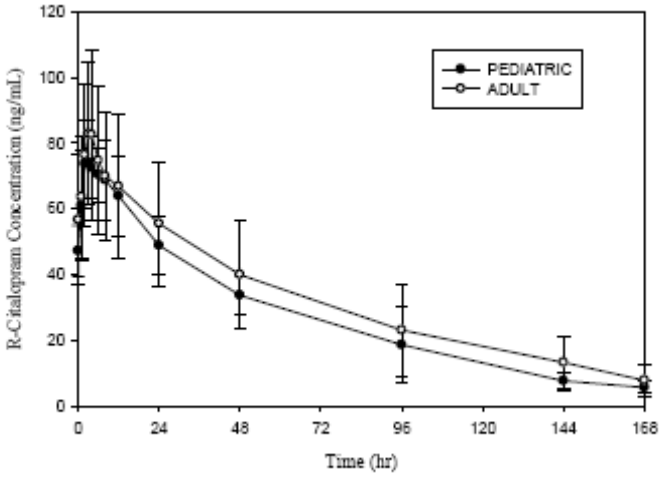


Table 3.	Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following Multiple Dose Administration of 40 mg Citalopram in Adult and Pediatric Patients (excluding 10 year-old female patient)		
	Escitalopram		
PK Parameters	Adult (N = 11)	Pediatric (N = 11)	p value
C_{max} (ng/mL)	57.2 ± 21.2	45.8 ± 13.7	0.293
T_{max} (hr)	2.8 ± 0.6	2.6 ± 1.4	0.384
AUC_{ss} (ng•h/mL)	925.7 ± 434.9	738.5 ± 283.0	0.358
$t_{½}$ (hr)	31.4 ± 9.8	29.1 ± 12.5	0.470
CL/F (L/hr)	26.5 ± 12.1	30.6 ± 11.10	0.358
Vz/F (L)	1075.9 ± 353.9	1297.5 ± 844.9	0.948
Ae_{0-24} (mg)	3.5 ± 2.4	2.3 ± 1.4	0.221

Table 4.	Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following a Multiple Dose Administration of 40 mg Citalopram in Female and Male Patients (excluding 10 year-old female patient)		
	Escitalopram		
PK Parameters	Female (N = 11)	Male (N = 11)	p-value
C_{max} (ng/mL)	53.4 ± 16.2	49.6 ± 20.9	0.511
T_{max} (hr)	2.8 ± 0.8	2.6 ± 1.3	0.217
AUC_{ss} (ng•h/mL)	885.9 ± 327.2	778.3 ± 418.5	0.264
$t_{½}$ (hr)	31.9 ± 11.3	28.5 ± 11.0	0.393
CL/F (L/hr)	23.5 ± 11.7	31.4 ± 13.0	0.264
Vz/F (L)	1012.3 ± 493.8	1269.2 ± 833.5	0.896
Ae_{0-24} (mg)	3.1 ± 1.9	2.9 ± 2.2	0.683

Table 5. Individual and Mean Pharmacokinetic Parameters of R-Citalopram for Pediatric Patients (excluding 10 year old female patient) after Administration of a Single Dose of 20 mg and Multiple Daily Dose of 40 mg/day Citalopram

				Single Dose			Multiple Dose						
AGE	Subject	SITE	SEX	Tmax	Cmax	AUC_{0-24}	Ae_{0-24}	Cmax	Tmax	t½	AUCss	Vz/F	CL/F
				(hr)	(ng/mL)	(ng•h/mL)	(mg)	(ng/mL)	(hr)	(hr)	(ng•h/mL)	(L)	(L/hr)
Pediatric	32	1	F	6.0	14.7	233.4	7.1	84.2	8.0	42.4	1754.4	697.5	11.4
Pediatric	29	2	F	4.0	11.2	170.8	3.6	77.6	1.0	39.5	1537.6	741.3	13.0
Pediatric	30	2	F	3.0	15.9	256.1	NA	68.8	4.0	62.3	1487.3	1208.3	13.4
Pediatric	31	2	F	6.0	15.4	244.7	6.1	91	3.0	33	1553.8	612.2	12.8
Pediatric	26	1	M	2.0	15.3	261.6	8.2	84.7	1.0	43.1	1418.5	875.9	14.1
Pediatric	28	1	M	4.0	11.5	189.6	3.3	66.4	3.0	35.6	1372.8	748.6	14.6
Pediatric	29	1	M	2.0	22.5	328	5.2	106.5	2.0	40.6	1974.5	593.2	10.1
Pediatric	30	1	M	4.0	12.5	196.6	4.9	70.3	6.0	38	1371.2	799.8	14.6
Pediatric	26	2	M	4.0	13.2	248	5.3	61.2	4.0	65.8	1038.7	1828.6	19.3
Pediatric	27	2	M	2.0	11.3	175	4.6	72.5	1.0	43.9	1350.1	958.6	14.8
Pediatric	28	2	M	4.0	11.2	168.4	NA	73.9	6.0	49.4	1563.7	912.1	12.9
			Mean	3.7	14.1	224.7	5.4	77.9	3.5	44.9	1493.0	905.1	13.7
			SD	1.4	3.3	49.6	1.6	12.9	2.3	10.5	239.3	351.5	2.3
			Min	2.0	11.2	168.4	3.3	61.2	1.0	33.0	1038.7	593.2	10.2
			Max	6.0	22.5	328.0	8.2	106.5	8.0	65.8	1974.5	1828.6	19.3
			CV%	38.1	23.8	22.1	29.3	16.6	66.0	23.3	16.0	38.8	16.9

COMMENTS:

No age or gender effects on pharmacokinetic parameters were found for escitalopram. Exclusion of the 10 yr old subject had no impact on the results comparing adults and pediatrics.

STUDY NO. SCT-PK-10-A SINGLE DOSE PHARMACOKINETIC STUDY OF ESCITALOPRAM IN HEALTHY ADOLESCENT AND ADULT SUBJECTS

OBJECTIVE

To assess tolerability and compare the pharmacokinetics of escitalopram, S-enantiomer of the racemic compound citalopram (CIT), following a single dose regimen in healthy adolescents and adults**.**

DESIGN OF STUDY

This was a single-center, open-label, single-dose study in twenty-four (24) subjects. Twelve (12) adolescents and twelve (12) adults received a 10 mg **escitalopram (S-isomer of CIT)** oxalate tablet on Day 1. Subjects were institutionalized for the duration of the study. The study was carried out from June 23, 2002 to June 30, 2002. The parent or guardian of the adolescent subjects accompanied them during the study. Study drug was dosed with 240 mL of water under fasted conditions. Standardized, bland, low-fat meals were provided to all subjects while institutionalized.

Concurrent Medications
No concomitant medication was permitted during the study. Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. They were specifically reminded that this included aspirin, Bufferin®, Excedrin®, Anacin®, ibuprofen, acetaminophen, other over-the-counter analgesics, vitamin preparations, cough syrup, herbal remedies, and homeopathic medicines.

Subject Demographics

Group	Subject No.	Gender	Race	Height (cm)	Weight (kg)	Age (yrs)
Adolescent	1	F	White	154.9	50.9	15
Adolescent	2	F	White	154.9	51.4	15
Adolescent	3	F	Other	162.6	66.4	14
Adolescent	4	F	White	149.9	49.5	12
Adolescent	5	F	Other	152.4	51.8	16
Adolescent	6	F	White	160.0	49.1	14
Adolescent	7	M	White	162.6	69.1	15
Adolescent	8	M	White	162.6	50.5	13
Adolescent	9	M	White	167.6	69.1	14
Adolescent	10	M	White	175.3	88.6	17
Adolescent	11	M	Black	160.0	46.4	15
Adolescent	12	M	Other	172.7	77.3	17
			Mean	161.3	60.0	14.8
			SD	7.8	13.7	1.5
			Range	149.9-175.3	46.4-88.6	12-17
Adult	21	F	White	172.7	81.8	27
Adult	22	F	White	162.6	70.0	33
Adult	23	F	Other	160.0	66.4	30
Adult	24	F	Other	154.9	63.6	34
Adult	25	F	White	154.9	54.1	29
Adult	26	F	White	157.5	63.6	35
Adult	27	M	White	172.7	71.8	28
Adult	28	M	White	185.4	75.5	29
Adult	29	M	White	160.0	73.6	35
Adult	30	M	Black	175.3	55.9	22
Adult	31	M	White	167.6	60.9	23
Adult	32	M	White	177.8	72.7	35
			Mean	166.8	67.5	30.0
			SD	10.0	8.2	4.6
			Range	154.9-185.4	54.1-81.8	22-35

ANALYTICAL

Since the plasma concentrations of R-citalopram, R-demethylcitalopram, and Rdimethylcitalopram, and S-didemethylcitalopram levels were below the lower limit of quantitation (BLOQ) of the analytical assay in all subjects (BLOQ of 1 ng/mL), their validation will not be reported.

The study was carried out from June 23, 2002 to June 30, 2002.
Analysis August 2002
Total Storage 60 days

Parameter	S-Citalopram	S-demethyl-citalopram
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ	1 ng/ml	1 ng/ml

Linearity (Standard curve samples)	1-150 ng/ml	1-150 ng/ml
Quality Control (QC) Samples	3.00 ng/ml 30 ng/ml 120 ng/ml	3.00 ng/ml 30 ng/ml 120 ng/ml
Precision of Standards (%CV)	1.7% @ 1 ng/ml 1.1% @ 150 ng/ml	1.0% @ 1 ng/ml 1.6% @ 150 ng/ml
Precision of QC Samples (%CV)	2.4% @3.00 ng/ml 2.3% @ 120 ng/ml	1.7% @3.00 ng/ml 2.0% @ 120 ng/ml
Accuracy of Standards (%)	100% @ 1 ng/ml 99.7% @ 150 ng/ml	99% @ 1 ng/ml 99% @ 150 ng/ml
Accuracy of QC Samples (%)	99% @ 3 ng/ml 99% @ 120 ng/ml	97% @ 3.00 ng/ml 101% @ 120 ng/ml

Blood Sample Collection

Blood samples for the determination of S-citalopram, R-citalopram, S-demethylcitalopram, R-demethylcitalopram, S-didemethylcitalopram and R-didemethylcitalopram concentrations were collected following dosing on Day 1 at 0.0-hour (pre-dose), 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post dose.

PHARMACOKINETIC DATA ANALYSIS

Pharmacokinetic parameters were estimated using WinNonlin (version 3.3). The following parameters were determined from the plasma concentrations of escitalopram: the area under the plasma concentration versus time curve (AUC0-t and AUC0-∞), maximum plasma concentration (Cmax), time of maximum plasma concentration (Tmax), elimination half-life (T½), oral clearance (CL/F) and apparent volume of distribution (Vz/F). The following parameters were estimated for the metabolites: Cmax, Tmax, AUC0-t,AUC0-∞ and T½.

Maximum plasma concentration (Cmax) and the time of maximum concentration (Tmax) for escitalopram and its metabolites were determined by observation. The first-order rate constant, λz, describing the terminal decline in plasma was estimated by WinNonlin (version 3.3) using log-linear regression of the terminal

linear phase of the mean plasma concentration-time curves. A minimum of 3 points in the terminal phase were required to define λz.

RESULTS

ADVERSE EVENTS

The incidence of adverse events is provided in Table 1.

There were no serious adverse events reported. No subject withdrew from the study due to treatment emergent adverse event (TEAE). Seven (29.2%) of the twenty-four subjects, 2 adolescent and 5 adult subjects, reported a total of 10 adverse events. The adverse events reported were nausea, headache, dizziness, vomiting, and diarrhea and they were all mild in intensity.

Table 1 . Incidence of Treatment Emergent Adverse Events (% Subjects)

Preferred Term	*Adolescents (N=12) n (%)*	*Adults (N=12) n (%)*
Subjects with at least one TEAE	2 (16.7)	5 (41.7)
Nausea	0 (0)	3 (25.0)
Headache	0 (0)	1 (8.3)
Diarrhea	0 (0)	2 (16.7)
Dizziness	1 (8.3)	1 (8.3)
Vomiting	1 (8.3)	1 (8.3)

Figure 1. Mean Plasma Concentrations of S-citalopram Following Administration of a Single 10 mg Dose of Escitalopram Oxalate Tablet in Adolescent and Adult Subjects

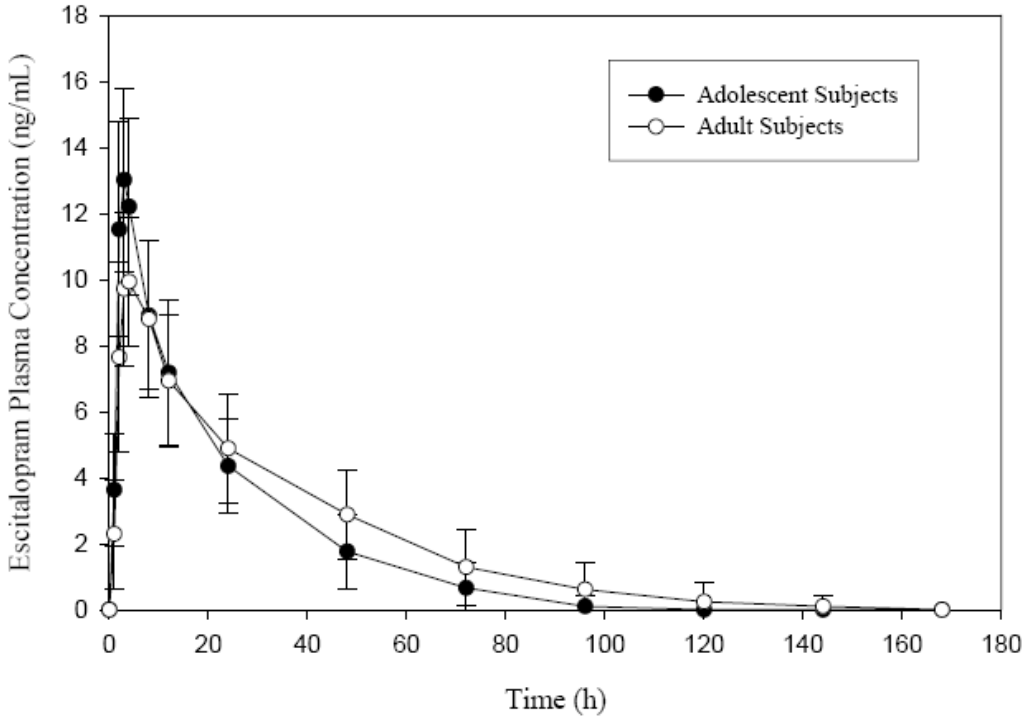


Table 2. Pharmacokinetic Parameters of Escitalopram Following Administration of a Single 10 mg Escitalopram Oxalate Tablet in Healthy Adolescent Subjects

Subject	C_{max} *(ng/mL)*	T_{max} *(h)*	AUC_{0-t} *(ng h/mL)*	$AUC_{0-\infty}$ *(ng h/mL)*	$T_{1/2}$ *(h)*	*CL/F (L/h)*	*Vz/F (L)*
1	11.50	3	197.5	224.9	16.0	44.5	1025.0
2	14.75	3	174.8	232.8	11.9	43.0	739.2
3	11.80	3	191.6	217.0	16.3	46.1	1085.2
4	10.78	2	113.8	143.3	10.6	69.8	1066.9
5	13.86	3	235.2	265.0	15.3	37.7	833.9
6	18.92	3	433.5	467.2	18.8	21.4	581.4
8	16.07	2	410.6	462.4	22.6	21.6	704.3
9	12.79	3	299.1	335.8	22.5	29.8	966.7
10	9.18	3	331.6	381.4	32.2	26.2	1218.6
11	13.61	3	276.8	319.1	16.1	31.3	728.5
12	10.85	4	322.9	379.9	26.5	26.3	1005.7
Mean	13.10	2.9	271.6	311.7	19.0	36.2	905.0
SD	2.76	0.5	100.0	105.0	6.4	14.3	198.5
%CV	21.10	18.5	36.8	33.7	33.9	39.5	21.9
Minimum	9.18	2.0	113.8	143.3	10.6	21.4	581.4
Maximum	18.92	4.0	433.5	467.2	32.2	69.8	1218.6

Table 3. Pharmacokinetic Parameters of Escitalopram Following Administration of a Single 10 mg Escitalopram Oxalate Tablet in Healthy Adult Subjects

Subject	C_{max} *(ng/mL)*	T_{max} *(h)*	AUC_{0-t} *(ng h/mL)*	$AUC_{0-\infty}$ *(ng h/mL)*	$T_{1/2}$ *(h)*	*CL/F (L/h)*	*Vz/F (L)*
21	8.52	3	142.2	171.2	19.4	58.4	1630.9
22	9.98	4	282.9	323.2	23.9	30.9	1066.6
23	11.14	4	269.4	306.6	24.1	32.6	1135.6
24	10.75	4	345.9	402.1	24.7	24.9	884.6
25	13.78	3	546.2	603.2	35.9	16.6	858.8
26	10.92	8	393.9	441.5	29.8	22.6	972.4
27	7.69	2	181.9	360.0	48.4	27.8	1939.8
28	11.91	3	399.8	439.6	27.6	22.7	905.5
29	8.53	4	162.3	194.5	18.7	51.4	1389.5
30	12.33	3	638.1	711.9	44.1	14.0	894.0
31	7.83	8	203.0	260.4	21.6	38.4	1197.8
32	11.32	8	388.8	430.7	28.2	23.2	945.1
Mean	10.39	4.5	329.5	387.1	28.9	30.3	1151.7
SD	1.92	2.2	154.2	157.0	9.4	13.4	340.6
%CV	18.44	48.8	46.8	40.6	32.7	44.1	29.6
Minimum	7.69	2.0	142.2	171.2	18.7	14.0	858.8
Maximum	13.78	8.0	638.1	711.9	48.4	58.4	1939.8

Figure 2. Mean Plasma Concentrations of S-Demethylcitalopram Following Administration of a Single 10 mg Dose of Escitalopram Oxalate Tablet in Adolescent and Adult Subjects

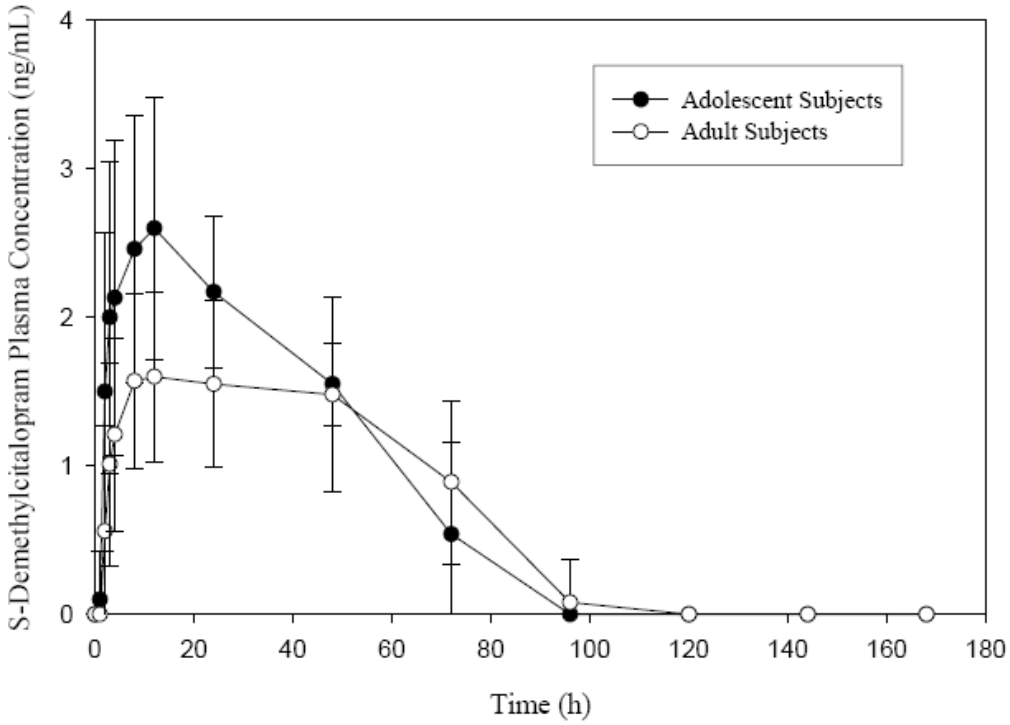


Table 4. Pharmacokinetic Parameters of S-Demethylcitalopram Following Administration of a Single 10 mg Escitalopram Oxalate Tablet in Healthy Adolescent Subjects

Subject	C_{max} *(ng/mL)*	T_{max} *(h)*	AUC_{0-t} *(ng h/mL)*	$AUC_{0-\infty}$ *(ng h/mL)*	$T_{1/2}$ *(h)*
1	3.21	8.0	109.2	198.2	39.5
2	4.31	12.0	141.7	ND	ND
3	2.70	8.0	96.3	171.1	39.0
4	3.20	3.0	110.5	173.3	31.3
5	2.94	12.0	147.0	232.6	48.3
6	3.17	12.0	158.2	261.5	51.9
8	1.92	12.0	113.1	228.2	70.6
9	1.64	24.0	96.2	ND	ND
10	1.34	12.0	49.8	ND	ND
11	3.09	12.0	147.1	216.2	42.7
12	1.71	12.0	73.0	ND	ND
Mean	2.66	11.5	112.9	211.6	46.2
SD	0.90	5.0	33.7	33.0	12.7
%CV	33.82	43.7	29.9	15.6	27.4
Minimum	1.34	3.0	49.8	171.1	31.3
Maximum	4.31	24.0	158.2	261.5	70.6

ND = Not determined

Table 5. Pharmacokinetic Parameters of S-Demethylcitalopram Following Administration of a Single 10 mg Escitalopram Oxalate Tablet in Healthy Adult Subjects

Subject	C_{max} *(ng/mL)*	T_{max} *(h)*	AUC_{0-t} *(ng h/mL)*	$AUC_{0-\infty}$ *(ng h/mL)*	$T_{1/2}$ *(h)*
21	2.37	8.0	81.2	172.3	50.1
22	1.92	12.0	113.2	280.3	92.7
23	1.84	24.0	111.3	ND	ND
24	2.18	24.0	160.9	243.4	57.1
25	1.51	12.0	92.9	589.9	284.7
26	1.84	8.0	107.8	231.5	76.5
27	3.00	48.0	157.2	ND	ND
28	1.43	12.0	90.7	ND	ND
29	1.83	12.0	68.8	ND	ND
30	0.00	0.0	0.0	ND	ND
31	1.65	24.0	97.3	ND	ND
32	1.49	48.0	89.7	ND	ND
Mean	1.76	19.3	97.6	303.5	112.2
SD	0.71	15.2	41.4	164.8	97.8
%CV	40.23	78.8	42.4	54.3	87.2
Minimum	0.00	0.0	0.0	172.3	50.1
Maximum	3.00	48.0	160.9	589.9	284.7

ND = Not determine

COMMENTS:

Following a single 10 mg dose adolescents had a 26% higher Cmax and a 19% lower AUC than adults.

STUDY CIT_PK_13 AN EVALUATION OF THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF CITALOPRAM IN PEDIATRIC AND ADULT SUBJECTS

PURPOSE OF THE STUDY

This study was designed to evaluate the pharmacokinetics of citalopram and its metabolites in pediatric subjects (compared to adult subjects) following a single 20 mg dose.

STUDY PLAN

This was an open-label, parallel, single dose study in 12 pediatric (7 -11 years old) and 12 adult (18 - 35 years old) healthy male and female subjects. Subjects were institutionalized for the entire study. The parent or guardian of the pediatric subject accompanied the institutionalized subject during the study. Subjects received 20 mg of citalopram in a 10 mL oral solution (10mg/5 ml) at 0800 on Study Day 1.

Multiple plasma samples were obtained on Study Day 1. On Study Days 2 through 8, subjects had a single blood draw at 0800 hours.

METHODS

DEMOGRAPHICS

	Adults N=12	Children N=12
Age, years		
Mean	30.3	9.4
Standard Deviation	3.8	1.1
Min – Max	23, 35	7,11
Weight, kg		
Mean	74	34
Standard Deviation	16.43	5.17
Min – Max	52.7, 102.7	26.8, 44.1
Height, cm		
Mean	165.1	137.0
Standard Deviation	12.11	7.28
Min – Max	149.9, 188	127.0, 149.9

Eight adults were Caucasian, and four were non-Caucasian (Black). Ten children were Caucasian, and 2 were non-Caucasian (Black).

Treatment Regimen

On Day 1 subjects received a single 20 mg dose of citalopram in a 10 mL oral solution (10mg/10mL) at 0800 hours. Subjects remained ambulatory or seated

upright and awake for the first four (4) hours following drug administration and did not engage in strenuous activity.

Diet
Subjects were dosed under fasted conditions. During the study, standardized, bland, lowfat meals were provided to all subjects while institutionalized.

Concomitant Medication
No concomitant medication was permitted during the study. Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. They were specifically reminded that this included aspirin, Bufferin®, Excedrin®, Anacin®, ibuprofen, acetaminophen, other over-the-counter analgesics, vitamin preparations, cough syrup, herbal remedies and homeopathic medicines

Blood Sampling and Collection Procedure
Blood samples were collected at the following times.
Day 1, after 0800 drug administration at: 0 hour (pre-dose), 1, 2, 3, 4, 8, and 12 hours (post-dose) Days 2, 3, 4, 5, 6, 7, and 8 at: 24, 48, 72, 96, 120, 144, and 168 hours (post Day 1 dose).

ANALYTICAL

Parameter	R-Citalopram	S-Citalopram	S-demethyl-citalopram	S-didemethyl citalopram
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ	1 ng/ml	1 ng/ml	1 ng/ml	1 ng/ml
Linearity (Standard curve samples)	1-150 ng/ml	1-150 ng/ml	1-150 ng/ml	1-150 ng/ml
Quality Control (QC) Samples	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml
Precision of Standards (%CV)	1.0% @ 1 ng/ml 2.3% @ 150 ng/ml	1.4% @ 1 ng/ml 4.3% @ 150 ng/ml	4.6% @ 1 ng/ml 4.6% @ 150 ng/ml	5.3% @ 1 ng/ml 4.0% @ 150 ng/ml
Precision of QC Samples (%CV)	6% @3.75 ng/ml 3.6% @ 75 ng/ml	6.4% @3.75 ng/ml 3.4% @ 75 ng/ml	7.7% @3.75 ng/ml 8.2% @ 75 ng/ml	6.3% @3.90 ng/ml 7.0% @ 78 ng/ml

Accuracy of Standards (%)	99% @ 1 ng/ml 101% @ 150 ng/ml	99.2% @ 1 ng/ml 102% @ 150 ng/ml	99.6% @ 1 ng/ml 99.3% @ 150 ng/ml	99% @ 1 ng/ml 101% @ 150 ng/ml
Accuracy of QC Samples (%)	99% @ 1 ng/ml 94% @ 75 ng/ml	99% @ 1 ng/ml 94% @ 75 ng/ml	97.2% @ 1 ng/ml 94% @ 75 ng/ml	94@3.75 ng/ml 92%@75 ng/ml

DATA ANALYSIS

Plasma concentrations of citalopram, DCT and DDCT were derived from the concentration values for R-CT, escitalopram, R-DCT, S-DCT, R-DDCT, and S-DDCT. The area under the plasma concentration time curve (AUC0-t and AUC0-∞), maximum plasma concentration (Cmax), time of maximum plasma concentration (Tmax), and elimination half-life (T½) were obtained from the plasma concentrations. The areas under the plasma concentration versus time curves up to the last measurable concentration (AUC0-t) were estimated by numerical integration using the linear trapezoidal rule.

STATISTICAL EVALUATION

Pharmacokinetic Parameter

Estimates of mean values obtained for pharmacokinetic parameters were compared statistically between age and gender groups using standard statistical procedures.

Statistical analyses were performed with the Statistical Analyses System (SAS) version 6.12 for the UNIX system microcomputers using the General Linear Models procedure (GLM). Analysis of variance (ANOVA) was performed on all of the pharmacokinetic parameters, including Cmax, AUC, Tmax, T½, and CL/F. AUC and Cmax were logtransformed in the analysis of variance comparison.

RESULTS

Table 1. Incidence of Treatment Emergent Adverse Events

Preferred Term	Adults (N=12) n (%)	Children (N=12) n (%)
Patients with at least one TEAE	7 (58.3)	5 (41.7)
Nausea	5 (41.7)	5 (41.7)
Headache	5 (41.7)	1 (8.3)
Diarrhea	2 (16.7)	2 (16.7)
Dizziness	1 (8.3)	0 (0)
Chills	1 (8.3)	0 (0)
Fever	0 (0)	1 (8.3)
Vomiting	0 (0)	4 (33.3)

Pharmacokinetic data were analyzed for all 24 subjects [12 adults (9 females and 3 males) and 12 children (6 males and 6 females)] who entered the study.

Table 2. Pharmacokinetic Parameters (Mean ± SD) of Citalopram following Administration of 20 mg Citalopram in Healthy Adult and Pediatric Volunteers.

Citalopram			
PK Parameters	Adult (N=12)	Pediatric (N=12)	p
C_{max} (ng/mL)	20.5 ± 4.7	43.8 ± 8.4	0.000
T_{max} (hr)	3.8 ± 0.5	2.9 ± 0.8	0.002
AUC_{0-t} (hr* ng/mL)	805.8 ± 289.9	1110.1 ± 336.5	0.012
AUC_{0-inf} (hr* ng/mL)	871.5 ± 312.4	1161.7 ± 343.4	0.018
$t_{½}$ (hr)	34.2 ± 7.6	26.1 ± 4.0	0.007
CL/F (L/hr)	25.4 ± 8.0	18.3 ± 4.2	0.009
Vz/F (L)	1189.2 ± 234.0	675.0 ± 133.5	0.000

Following a single dose administration of 20 mg citalopram oral solution, a shorter Tmax (24%, i.e., 54 minutes), higher Cmax (2 fold), larger AUC0-t (38%) and AUC0-inf (33%) were observed in children compared to adults (Table 2). These data suggest that the rate of absorption of citalopram was faster and the extent of absorption was higher in children compared to adults. Also, a shorter t½ (24%, i.e., 8 hrs) and smaller CL/F (28%) and Vz/F (43%) were observed in children compared to adults.

OVERALL COMMENT:

The firm has conducted several studies measuring different citalopram moieties which makes a direct comparison between studies related to exposure difficult.

However for study cit-pk-07 the firm did conduct a steady-state study for 3 weeks at 40 mg/day in patients. The graph of AUC0-24 hrs vs percentile for the single dose study showed a slight increase in exposure of S-citalopram for pediatrics 210 ng/mlxhr vs 260 ng/mlxhr Figure 1. However the comparable graph following steady-state dosing at 40mg/day for 3 weeks was reversed Figure 2. The reversal may be due to the fact that the drug has a 35 hr half-life but the single dose measurements were only to 24 hrs. Since the prescribed dosage regimen is multiple dosing, the reviewer has concluded that the increased exposure following single dosing is not relevant. Exposure for children is similar to adults for approximately 75-80% of the subjects (N=24) in the study.

Figure 1. AUC0-24hrs vs. percentile for adults and children in Study 07 following a single 20 mg/day dose.

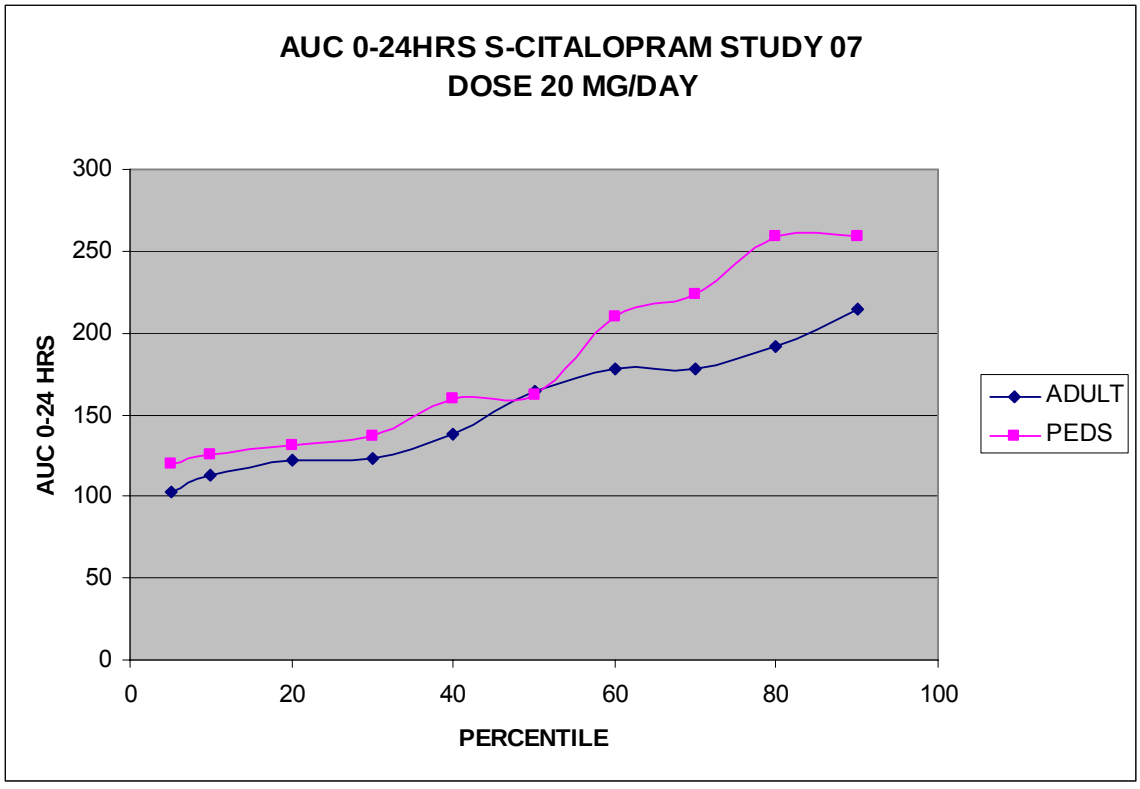
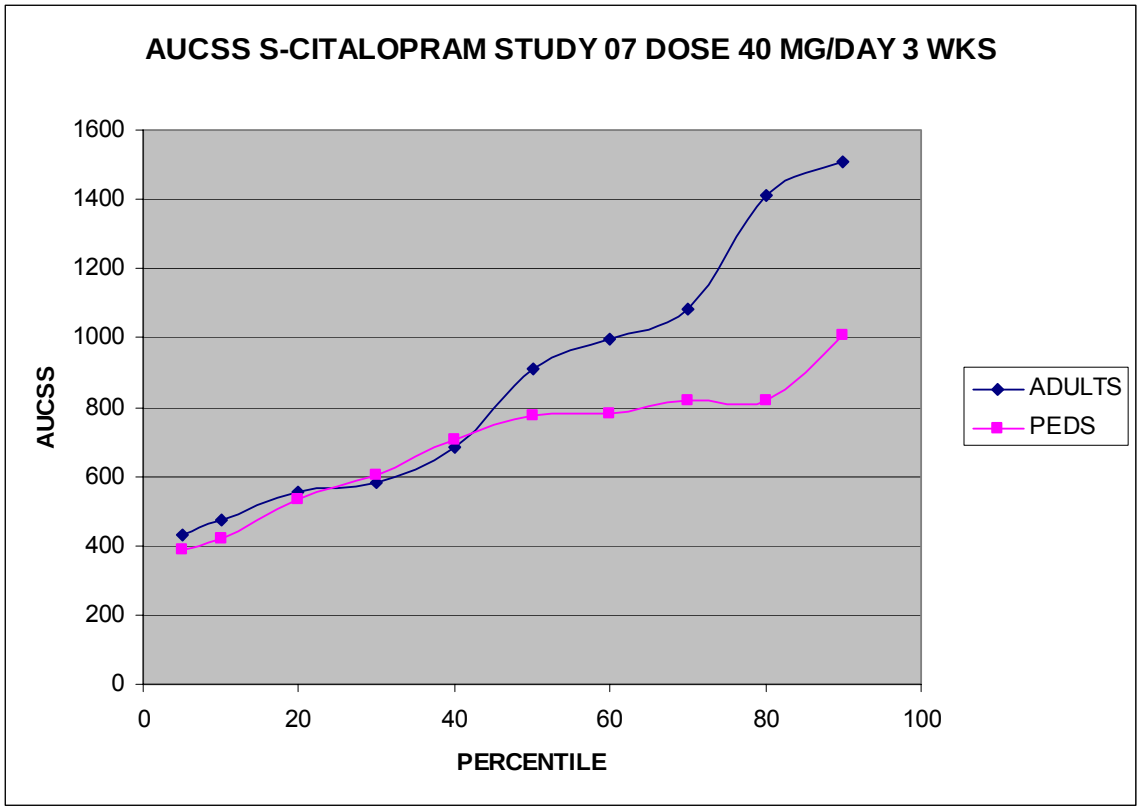


Figure 2. AUCss vs. percentile for adults and children in Study 07 following a single (last dose) 40 mg/day dose for 3 weeks.



SIGNATURES

Andre Jackson_____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 21-323, HFD-860(Mehta, Raman, Baweja, Jackson)
C:\Data\REVIEWS\NDA\LEXAPRO_NDA21323FOREST\PKCHILDREN.doc

5 pages withheld immediately after this page as B4 (draft labeling)

LABELING COMMENT:

OCP has proofed the PLR and it is acceptable.

LEXAPRO CURRENT LABEL

(b) (4)

LEXAPRO PLR LABEL

(b) (4)

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

/s/

Andre Jackson
2/20/2009 06:42:26 AM
BIOPHARMACEUTICS

Raman Baweja
2/20/2009 10:13:08 AM
BIOPHARMACEUTICS
Review also linked to NDA 21323/S-31, and NDA 21365/S-22.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

OTHER REVIEW(S)

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 21-323 21-365 BLA#	NDA Supplement:S- 030/031 021/022 BLA STN #	Efficacy Supplement Type SE- 5
Proprietary Name: Lexapro Established/Proper Name: escitalopram oxalate Dosage Form: tablets and oral solution Strengths:		
Applicant: Forest Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: May 22, 2008 Date of Receipt: May 23, 2008 Date clock started after UN:		
PDUFA Goal Date: March 23,2009	Action Goal Date (if different):	
Filing Date: July 21, 2008 Date of Filing Meeting: July 8, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): acute and long term treatment of MDD in adolescents		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***		☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***		☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR

	601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☐ YES # years requested: ☒ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐ Not applicable ☐ YES ☒ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ YES ☐ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☐ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	☒ YES ☐ NO

Note: *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☒ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** ☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use ☒ MedGuide ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☐ YES ☒ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**:	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☒ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☒ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 8, 2008

NDA/BLA #: 21-323/S-030/S-031
21-365/S-021/S-022

PROPRIETARY/ESTABLISHED NAMES: Lexapro

APPLICANT: Forest Pharmaceuticals

BACKGROUND: The sponsor has submitted a supplement to study Lexapro in adolescents ages 12-17.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Renmeet Grewal	y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Ni Khin		Y
Clinical	Reviewer:	Roberta Glass	Y
	TL:	Ni Khin	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Andre Jackson	Y
	TL:	Ray Baweja	Y
Biostatistics	Reviewer:	George Kordzakhia	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Nallaperumal Chidambaram	Y
	TL:		
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☐ NO ☐ YES ☐ NO

FACILITY (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Thomas Laughren, M.D.

GRMP Timeline Milestones:

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

Renmeet Grewal
3/3/2009 03:53:48 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: January 29, 2009

From: Jeanine Best, MSN, RN, PNP
Regulatory/Labeling Reviewer
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Psychiatric Products (DPP)

Drug: Lexapro (escitalopram oxylate), NDAs 21-323/S-030,031 and 21-365/S-021,022

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Lexapro labeling

BACKGROUND

The Maternal Health Team (MHT) and the Division of Psychiatric Products have a pilot program to work together to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of psychiatric drug product labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

As part of the MHT/DPP pilot labeling program of Pregnancy and Nursing Mothers labeling, the MHT reviewed and suggested revisions to the Pregnancy and Nursing Mothers subsections of Lexapro Labeling for pending supplemental application submitted to support treatment of adolescent patients with major depressive disorder. Lexapro (escitalopram) is a selective serotonin reuptake inhibitor (SSRI) currently indicated for the treatment of major depressive disorder (MDD) and generalized anxiety disorder in adult patients.

SUMBMITTED MATERIAL
Revised Lexapro labeling submitted December 24, 2008, to support labeling claim for acute and long-term treatment of adolescent patients (12 to 17 years) with major depressive disorder (MDD). Below is the current Pregnancy and Nursing Mothers labeling for Lexapro.

Highlights

Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus or child (8.3, 8.10).

8 USE IN SPECIFIC POPULATIONS

8.1 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 ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect

dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis).

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

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

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

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

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

Pregnancy-Nonteratogenic Effects
Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see Warnings and Precautions (5.2)].

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1—2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [see Dosage and Administration (2.2)]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

(b) (4) *is excreted in human breast milk.* (b) (4) *two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding 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.* (b) (4)

PREGNANCY SUBSECTION DISCUSSION

A literature search found no additional information from the published literature that would substantially enhance the safety data already included in the pregnancy subsection of the labeling.

NURSING MOTHERS SUBSECTION DISCUSSION

A summary of limited human data on use of escitalopram during lactation from published literature suggests that maternal doses of escitalopram up to 20 mg produce low amounts in milk with an estimate that exclusively breastfed infants would receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal-adjusted dose desmethylcitalopram. The absolute infant dose with escitalopram is about 40% less than data obtained from small lactation studies with racemic citalopram.

Rampona, et al,[1] studied the drug transfer of escitalopram and its demethyl metabolite (demethylcitalopram) into milk in eight lactating women taking 10 to 20 mg escitalopram daily, assessed the absolute and relative infant doses via milk, and also assessed breastfed infant adverse events. Six to eight milk steady-state milk samples were analyzed over a 24-hour interval after administration of a single 10 to 20 mg dose of escitalopram. The average escitalopram dose that an exclusively breastfed infant would receive was estimated to be 7.6 mg/kg of escitalopram (3.9% of maternal weight-adjusted dose) and 3 mcg/kg of desmethylcitalopram (1.7% of maternal weight-adjusted dose) daily. Escitalopram and desmethylcitalopram was undetectable in three of the breastfed infants (<1 mcg/L) and were less than 5 mcg/L in five infants (the mothers' serum levels of averaged 24 mcg/L of escitalopram and 20 mcg/L of desmethylcitalopram).

Rampona, et al, also looked at pooled analyses of racemic citalopram levels from published and unpublished studies and found that 18 mothers taking racemic citalopram at 20 to 60 mg daily had an average milk citalopram level of 157 mcg/L. Using this data, the authors estimated that an exclusively breastfed infant would receive 7.9% of the maternal weight-adjusted dose of citalopram.

Rampona, et al, did not see any adverse effects in the eight breastfed infants exposed to 10 to 20 mg of maternal escitalopram; however, there is one published case of necrotizing enterocolitis in a 5-day old infant following escitalopram exposure in-utero and with breast milk (the mother took escitalopram 20 mg daily through the pregnancy). Potts, et al,[2] hypothesis that escitalopram exposure may have been responsible for the necrotizing enterocolitis because of the effect of escitalopram on platelet aggregation and the pathogenesis of necrotizing enterocolitis related to intestinal platelet aggregation.

There are two reports in the Lexapro labeling of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; however Lee, et al,[3] conducted a prospective, observational cohort study to determine the frequency of infant adverse events from breast-milk exposure to maternal citalopram therapy. Breast-feeding women were divided into three groups based on their citalopram use. No statistically significant difference in the rate of infant adverse events in the three groups was found leading the authors to conclude that the benefits of breastfeeding outweigh the risks of citalopram breast-milk exposure but that infants should be monitored for possible side effects.

[1] Rampono J, Hackett, LP, Kristensen JH, Kohan R, Page-Sharp M, Ilett KF. Transfer of escitalopram and its metabolite demethylescitolopram into breast milk. Br J Clin Pharmocol. 2006 Sep;62(3)316-22.

[2] Potts, AL, Young KL, Carter BS, Shenai JP. Necrotizing enterocolitis associated with in utero and breast milk exposure to the selective serotonin reuptake inhibitor, escitalopram. J Perinatol. 2007;27:120-2.

[3] Lee A, Woo J, Ito S. Frequency of infant adverse events that are associated with citalopram use during breast-feeding. Am J Obst Gyn. 2004;190:218-21.

RECOMMENDATIONS

Provided below are MHT's recommended revisions to the sponsors' proposed labeling. We suggest reorganizing subsection 8.1 Pregnancy as shown in order to present the data in a more clinically relevant format. For subsection 8.3 Nursing Mothers, we added limited published human lactation data on escitalopram, and revised the included lactation data on racemic citalopram. Appendix A of this review provides a track changes version of labeling that highlights all changes made.

Highlights

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus **(8.1)**.
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3).

8 USE IN SPECIFIC POPULATIONS

Pregnancy Category C

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

MHT Comment:

Available data on dose and exposure of escitalopram in breastfed infants should be added to nursing mothers labeling for escitalopram in order to guide healthcare providers and patients in decision-making regarding lactation.

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for Lexapro is provided on pages 6-9 of this review. Appendix A of this review also provides a track changes version of labeling.

Appendix A –

Track Changes Version of Labeling

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

/s/

Jeanine Best
1/29/2009 08:56:54 AM
DRUG SAFETY OFFICE REVIEWER

Karen Feibus
1/29/2009 12:26:58 PM
MEDICAL OFFICER
I agree with the content, conclusions, and recommendations of this review

Lisa Mathis
2/4/2009 01:39:52 PM
MEDICAL OFFICER

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: January 23, 2009

TO: Renmeet Grewal, Regulatory Project Manager
Ni Khin, Medical Officer (Team Leader)
Division of Psychiatry Products

FROM: John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-323 S-30/31; NDA 21-365 S-21/22

APPLICANT: Forest Laboratories, Inc.

DRUG: Escitalopram Oxalate (Lexapro) Tablets and Solution

NME: Not a new molecular entity (NME)

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Treatment of major depressive disorder in adolescents (age 12 - 17)

CONSULTATION REQUEST DATE: July 25, 2008

DIVISION ACTION GOAL DATE: March 2, 2009

PDUFA DATE: March 23, 2009

I. BACKGROUND

Major depression occurs in approximately 4 to 8 percent of adolescents and is twice more prevalent in girls than in boys. The condition impairs psychosocial functioning and increases the risk for substance abuse and suicide. Early onset of the disease in adolescence is associated with a high recurrence rate and is a major risk factor for major depressive disorder (MDD) in adulthood. Based on the adult experience, parmacotherapy of adolescent depression may be expected to be well tolerated and effective in reducing the incidence of serious negative clinical outcome.

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) approved in adults for many indications: MDD and generalized anxiety disorder (GAD) in the United States; and MDD, panic disorder (PD), and social anxiety disorder (SAD) in Europe. It is one of the two stereoisomers of citalopram, a compound approved for the treatment of depression in more than 70 countries around the world. In vitro studies have shown that escitalopram is over IOO-fold more potent in serotonin reuptake inhibition than its corresponding stereoisomer.

Pivotal Studies

- Study SCT-MD-32: *A double-blind flexible dose study of escitalopram in pediatric patients with major depressive disorder*

  This was a double-blind, randomized, placebo-controlled, parallel-group, flexible dose study to compare escitalopram to placebo in pediatric major depression. Over 300 adolescents (age 1217) meeting DSM-IV criteria for MDD (CDRS-R score 2: 45 and a CGI-S 2: 4) were enrolled at approximately 25 centers. Escitalopram (10 mg and 20 mg) or matching placebo were orally administered daily for up to II weeks which included 8 weeks of double-blind treatment and I week of double-blind taper. The change from baseline (Visit 3) to Week 8 in Children's Depression Rating Scale-Revised (CDRS-R) total score was used as the primary efficacy endpoint. Safety evaluation included clinical adverse events, laboratory tests, and electrocardiograms (ECG).

- Study SCT-MD-32A: *An open-label extension study of the safety and efficacy of escitalopram in pediatric patients with major depressive disorder*

  This was an open-label, multicenter, flexible-dose, 24-week extension study to Study SCT-MD32 to evaluate the long-term safety and efficacy of escitalopram in the treatment of adolescent depression involving approximately 400 patients and 50 centers. Patients of age 12-18 who completed Study SCT-MD-32 (or Study SCT-MD-33) were treated with oral escitalopram 10 or 20 mg daily for 24 weeks (no reference therapy). The change in the following scores (from baseline at start of the qualifying study) served as the primary efficacy endpoint: Children's Depression Rating Scale-Revised (CDRS-R), Clinical Global Impressions-Severity Scale (CGIS), Clinical Global Impressions-Improvement Scale (CGI-I), and Children's Global Assessment Scale (CGAS). Safety evaluation included clinical adverse events, laboratory tests, and ECG.

Inspection

Two clinical sites with the highest patient enrollment were selected for good clinical practice (GCP) inspection. The sites were the same for Study SCT-MD-32 and Study SCT-MD32A. For Study SCT-MD-32, the p-value becomes non-significant if the data obtained from site 012 (Arifulla Khan, Northwest Clinical Research Center, Bellevue, WA) are removed from the primary efficacy analysis.

II. INSPECTION RESULTS

The results of the GCP inspections are presented in Table 1 and are further discussed below. The following abbreviations are used in Table 1:

- NAI: no action indicated (no deviations from regulations)
- VAI: voluntary action indicated (no significant deviations from regulations)
- OAI: official action indicated (significant deviations from regulations)
- Field: field investigator's initial recommendation in classifying the inspection result
- Interim: CDER's interim classification
- Final: CDER's final classification at issuance of post-inspectional correspondence

Table 1: Inspection Summary

Clinical Study Site	Site Protocol Subjects	Inspection Dates	Result Classification		
			Field	Interim	Final
Arifulla Khan, MD Northwest Clinical Research Center 1900 116th Avenue NE Bellevue, WA 98004	Site 012 SCT-MD-32 SCT-MD-32A 20 subjects	Nov 17 - 25 2008	VAI	VAI	Pending
Michael McManus, MD PCSD-Feighner Research 1550 Hotel Circle North, Suite 270 San Diego, CA 92111	Site 015 SCT-MD-32 SCT-MD-32A 18 subjects	Nov 6 - 24 2008	VAI	VAI	Pending

1. Arifulla Khan, MD (Site 012):

Northwest Clinical Research Center
1900 116th Avenue NE
Bellevue, WA 98004

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, and adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
- Subjects:
  - SCT-MD-32: 25 subjects were screened, 20 enrolled, and 15 completed the study. Complete records were reviewed for all subjects completing the study. Of the 15 subjects completing the study, 10 continued into the extension study (Study SCT-MD-32A).

- SCT-MD-32A: 10 subjects enrolled and 7 completed this extension study. Complete records were reviewed for all subjects.

b. General observations and commentary: No major deficiencies were observed. Study oversight and monitoring (IRB, sponsor) appeared to be adequate. Form FDA 483 was issued for the following two minor, apparently isolated findings:

- In 4 subjects, a parent or guardian who meets protocol-defined criteria were not always present for efficacy assessment at each study visit. In 3 of the 4 subjects, the parent other than the parent identified per protocol accompanied the subject for efficacy assessment at some study visits.
- In one subject, efficacy assessment (suicidal ideation score, one item at one study visit) was changed without adequate explanatory documentation.

c. Assessment of data integrity: Data from this study site (Site 012, Studies SCT-MD-32 and SCT-MD-32A) appear reliable.

2. Michael McManus, MD (Site 015):

PCSD-Feighner Research
1550 Hotel Circle North, Suite 270
San Diego, CA 92111

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, and adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
- Subjects:
  - SCT-MD-32: 28 subjects were screened, 18 enrolled, and 16 completed the study. Complete records were reviewed for enrolled subjects. Of the 16 subjects completing the study, 9 continued into the extension study (Study SCT-MD-32A).
  - SCT-MD-32A: 9 subjects enrolled and 7 completed this extension study. Complete records were reviewed for all enrolled subjects.

b. General observations and commentary: All data for primary efficacy endpoint and adverse clinical events were verified and study oversight and monitoring (IRB, sponsor) appeared to be adequate. However, Form FDA 483 was issued for multiple GCP violations, of which the major items consist of the following apparent violations in Study SCT-MD-32:

- Failure to exclude subjects from study according to the study protocol (subject 3213 not excluded despite positive urine drug screen, subject 3222 not excluded despite major depressive episode less than 12 weeks)
- Incomplete source documentation of subject eligibility questionnaires (10 subjects): Source documentation was mostly complete (except for one or two minor questionnaire items), for all affected subjects.
- Failure to perform clinical monitoring according to the study protocol (subject 3222, Visit 4, ECG and urine drug screen not performed)
- Missing case report forms for subjects 3207 (visits 3, 13, termination visit), 3221

(termination visit), 3224 (termination visit), and 3225 (visits 3, 4, termination visit)

- Minor inconsistent or incomplete efficacy assessment (several subjects/visits) that do not appear to importantly affect data reliability

c. Assessment of data integrity: The inspection of this clinical site is noteworthy for a number of scattered minor violations of the study protocol and/or applicable GCP regulations. The findings indicate inadequate attention to records maintenance but do not suggest a systematic pattern that raises concerns about data reliability. Data from this study site (Site 015, Studies SCT-MD-32 and SCT-MD-32A) appear reliable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Minor deficiencies were observed at the two clinical sites selected for inspection in support of this NDA, and a Form FDA 483 was issued at both clinical sites. The observed deficiencies, however, do not suggest bias in study conduct and are not expected to importantly affect data reliability. The data from the two study sites inspected are considered acceptable in support of the proposed indication.

{See appended electronic signature page}

John Lee, MD
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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/s/

John Lee
1/26/2009 06:01:16 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
1/27/2009 06:29:17 AM
MEDICAL OFFICER

DSI CONSULT: Request for Clinical Inspections

Date: *See Appended Electronic Signature Page*

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2, HFD-47

Through: Thomas Laughren, M.D./Division of Psychiatry Products/HFD-130
Ni Khin, M.D./ Medical Team Leader

From: Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager
Division of Psychiatry Products/HFD-130

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21-323/S-030/S-031 & NDA 365/S-021/S-022
Sponsor/Sponsor contact information: Maricarmen Raposo
Phone: (201) 386-2013
Maricarmen.raposo@frx.com

Drug: Lexapro (escitalopram oxalate) tablets & Lexapro (escitalopram oxalate) solution
NME: No
Standard or Priority: Standard
Study Population < 18 years of age: 12-17 yrs
Pediatric exclusivity: yes

Inspection Summary Goal Date: January 9, 2009
Action Goal Date: March 2, 2009
PDUFA: March 23, 2009

II. Background Information

This is a supplemental NDA for use of Lexapro oral tablets and oral solution in the acute and longer-term maintenance treatment of Major Depressive Disorder in adolescent patients (12-17yrs.)

III. Protocol/Site Identification

See Table below for the Protocol Title/# of subjects enrolled and site address:

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Northwest Clinical Research Center 1900 116th Avenue NE Bellevue, WA 98004	32/ 32 A	19	Acute and Maintenance Treatment of MDD in adolescent patitents
PCSD-Feighner Research 1550 Hotel Circle North, Suite 270 San Diego, CA 92108 7807 Convoy St., Suite 100 San Diego, CA 92111	32/32 A	18	Acute and Maintenance Treatment of MDD in adolescent patitents

Please find a copy of clinical study report and the study protocol in the edr (NDA 21-323; supplement number 030).

IV. Site Selection/Rationale

We chose the centers that had the highest number of patients enrolled. The centers are the same for both Studies 32 and 32A. For study 32, if the observations obtained from **center 012** are removed from the primary efficacy analysis, the p-value becomes non-significant.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- _X_ Enrollment of large numbers of study subjects
- ____ High treatment responders (specify):
- _X_ Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

Should you require any additional information, please contact *Renmeet Grewal, Pharm.D.* at Ph: *301-796-1080 or Roberta Glass, MD* at Ph: 301-796-1075.

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/s/

Thomas Laughren
7/25/2008 03:08:24 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-323/S-030/S-031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Thursday, January 08, 2009 3:14 PM
To: 'Raposo, Maricarmen'
Subject: Z-scores for Lexapro supplements for adolescents

Hi Maricarmen,

Because of the high drop out rate of Study 32A, we are requesting further details for the z-scores of this study. Please provide the z-scores for weight for each patient by visit. If there is a missing visit, please do not assign it a score. Please also provide one graph representing the mean weight z-score by visit for each treatment group (i.e. escitalopram and placebo) based on the OC (observed cases) data set.

Please submit this information by January 15, 2009.

Thank you,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
1/8/2009 03:16:15 PM
CSO

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Thursday, December 04, 2008 2:58 PM
To: 'Raposo, Maricarmen'
Subject: Lexapro Peds MDD more z-score data request

Hi Maricarmen,

We appreciate your submission dated October 1, 2008 which includes z-score data for study 32A. At this point in the review, we will need additional z-score data sets for the following individual studies: Study SCT-MD-32, Study SCT-MD-15, and Study CIT-MD-18.

Please use the same format used in the October 1, 2008 submission (i.e. The data sets should each include one row for each patient, the study number, indication, age, gender, baseline weight and z-scores).

Also, please provide the following:
1. Composite z-score results for each study individually,
2. A pooled z-score analysis of all 8 week placebo controlled studies (32, 15, and 18), and
3. A pooled z-score analysis of all studies (32, 32A, 15, and 18).

Because of time restraints within this review process, we are requesting that you submit this data with in one week of receipt of this request. We appreciate your help with providing the above information which is very important to your application process.

Sincerely,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
12/4/2008 03:00:49 PM
CSO

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Thursday, September 11, 2008 3:21 PM
To: 'Raposo, Maricarmen'
Subject: Lexapro adolescent MDD information request

Dear Maricarmen,

As you are aware, investigators have used growth curve data to assess growth in open label studies, in some cases by using z-scores. A z-score is the number of standard deviations that one is from their gender/age standardized mean. Investigators determine each subject's z-score at the beginning and then at the end of the observation period. If the mean change in the z-score is negative, then the group did not grow as expected based on normal population data.

We note that you have provided a table summarizing the z-scores in the ISS of your pediatric submission of NDA 21323/21326. At this time, we are requesting that you provide an electronic data set for the long-term study (32A) for both the open-label and placebo controlled portions of the study. The data set should include one row for each patient, the study number, indication, age, gender, baseline weight and z-scores (prior to the controlled trial and baseline for the open-label phase), end of the open-label phase weight and z-scores, treatment and assigned dose. Please include the SAS program (or algorithm/formula) you used to derive the z scores.

Sincerely,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
9/11/2008 04:50:31 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-323/S-030/S-031
NDA 21-365/S-021/S-022

Forest Laboratories, Inc.
Attention: Maricarmen Raposo
Senior Associate, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Dear Ms. Raposo:

Please refer to your May 22, 2008 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) tablets (NDA 21-323) and Oral solution (NDA 21-365).

We also refer to your submissions dated June 12, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on July 21, 2008 in accordance with 21 CFR 314.101(a).

We request that you submit the following information:

- Please provide the revised calculation for the claim for categorical exclusion and how you arrived to this point.
- Submit Patent Information (form 3524a) with appropriate patent information.
- Please provide your proposed labeling (both clean and marked up version in Word) incorporating all changes which are clearly demarcated.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Renmeet Grewal, Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Mitchell Mathis
8/6/2008 03:55:21 PM
For Dr. Laughren

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
HFD- 710/Stat Attention: Peiling Yang			HFD-130/ Division of Psychiatry Products	
DATE 6-6-08	IND NO.	NDA NO. 21-323/ S-030 21-365/S-020	TYPE OF DOCUMENT New supplement for acute and long-term treatment of adolescent patients	DATE OF DOCUMENT 5-22-08 Stamp Date:5-23-08
NAME OF DRUG Lexapro (escitalopram oxalate)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: Filing mtg: 7/8/08 PDUFA date: 3/23/09

NAME OF FIRM: Forest Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a new supplemental NDA for the treatment of adolescent children (ages 12-17yrs) for the treatment of acute and long-term major depressive disorder. The label in PLR format for the first time. Attached is the link for the submission:
\\CDSESUB1\EVSPROD\NDA021323\021323.ENX
If you have any questions you can call me at 301-796-1080 or email at renmeet.grewal@fda hh.gov.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Renmeet Grewal, Pharm.D. Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Renmeet Grewal

6/6/2008 03:20:11 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
HFD- 860/Biopharm Attention: Raman Baweja			HFD-130/ Division of Psychiatry Products	
DATE 6-6-08	IND NO.	NDA NO. 21-323/ S-030 21-365/S-020	TYPE OF DOCUMENT New supplement for acute and long-term treatment of adolescent patients	DATE OF DOCUMENT 5-22-08 Stamp Date:5-23-08
NAME OF DRUG Lexapro (escitalopram oxalate)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: Filing mtg: 7/8/08 PDUFA date: 3/23/09

NAME OF FIRM: Forest Pharmaceuticals

REASON FOR REQUEST

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- ☐ NEW PROTOCOL
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- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

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\\CDSESUB1\EVSPROD\NDA021323\021323.ENX
If you have any questions you can call me at 301-796-1080 or email at renmeet.grewal@fda hh.gov.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Renmeet Grewal, Pharm.D. Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Renmeet Grewal

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