

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020822Orig1s038, s040

021046Orig1s016, s017

Trade Name: Celexa 10 mg, 20 mg, and 40 mg tablets
Celexa 10 mg/5 ml oral solution

Generic Name: Citalopram hydrobromide

Sponsor: Forest Laboratories, Inc.

Approval Date: August 12, 2011

Indications: Provide for a comprehensive Medication Guide and new QTc language in the Clinical Pharmacology, Contraindications, Warnings, Precautions/Drug Interactions, Adverse Reactions/ECG Changes, and Dosage And Administration sections of the Prescribing Information

CENTER FOR DRUG EVALUATION AND RESEARCH

020822Orig1s038, s040

021046Orig1s016, s017

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020822Orig1s038, s040

021046Orig1s016, s017

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020822/S-038/S-040
NDA 021046/S-016/S-017

SUPPLEMENT APPROVAL

Forest Laboratories, Inc.
Attention: Debleena Sengupta, Ph.D., RAC
Senior Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Sengupta:

Please refer to your Supplemental New Drug Applications (sNDA) dated March 31, 2010 (NDAs 020822/S-040, 021046/S-017), and May 15, 2009 (NDAs 020822/S-038, 021046/S-016), submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Celexa (citalopram hydrobromide) 10 mg, 20 mg, and 40 mg tablets (NDA 020822), and Celexa (citalopram hydrobromide) 10 mg/5 ml oral solution (NDA 021046).

We acknowledge receipt of your amendments dated April 1, 2010, July 13, 2010, November 24, 2010, June 28, 2011, and June 29, 2011.

The November 24, 2010, submission constituted a complete response to our September 24, 2010 complete response action letter for 020822/S-038 and 021046/S-016; and the June 28, 2011 submission constituted a complete response to our December 29, 2010 complete response action letter for 020822/S-040 and 021046/S-017.

The Prior Approval Labeling Supplements (020822/S-038 and 021046/S-016) provide for a comprehensive Medication Guide, as requested in an Agency letter dated April 16, 2009.

The Prior Approval Labeling Supplements (020822/S-040 and 021046/S-017) provide for new QTc language in the **Clinical Pharmacology, Contraindications, Warnings, Precautions/Drug Interactions, Adverse Reactions/ECG Changes, and Dosage And Administration** sections of the Prescribing Information.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text as communicated in an email dated August 10, 2011 between yourself and Bill Bender, of this Agency.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 Bill Bender, Regulatory Project Manager, at (301) 796-2145.

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

ENCLOSURE: Content of Labeling (package insert and Medication Guide)

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/s/

THOMAS P LAUGHREN
08/12/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020822Orig1s038, s040

021046Orig1s016, s017

OTHER ACTION LETTERS



NDA 20822/S-040, 21046/S-017

COMPLETE RESPONSE

Forest Laboratories, Inc.
Attention: Maricarmen Raposo,
Senior Associate Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Ms. Raposo:

We acknowledge receipt of your Supplemental New Drug Applications dated March 31, 2010, received on April 1, 2010 regarding NDAs 20822/S-040, Celexa (citalopram hydrobromide) 10 mg, 20 mg, and 40 mg tablets and 21046/S-017, Celexa (citalopram hydrobromide) 10 mg/5 ml oral solution.

We also acknowledge your amendment dated July 13, 2010, received on July 14, 2010 which provided the full clinical report of study CIT-PK-15.

These Prior Approval labeling supplements propose changes to safety information in the following section of the label:

- **Section 6 ADVERSE REACTIONS/ ECG Changes subsection**

We have completed the review of your applications and have determined that we cannot approve these applications in their present form.

Instead of incorporating the ECG changes in the “ADVERSE REACTIONS” section of the label, we believe that the ECG information need to be included in the “CONTRAINDICATIONS”, “WARNINGS AND PRECAUTIONS” and “DRUG INTERACTIONS” sections of the label. We have described our reasons for this action below and, where possible, our recommendations to address these issues. We have used **red strike through font for sections to be deleted** and **blue font underlined for the addition**.

- **Section 4 CONTRAINDICATIONS**

- **4.2 QT prolongation**

- Celexa is contraindicated in patients with congenital long QT syndrome

- **Section 5 WARNING AND PRECAUTIONS**

- **5.2 QT-prolongation and Torsade de Pointes**

Citalopram causes dose dependent QT prolongation. Torsade de Pointes has been reported post-marketing. Avoid in patients with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalation from 40 mg to 60 mg should be initiated with ECG monitoring in all patients and considered only in the absence of therapeutic alternatives. ECGs should be collected at baseline and periodically thereafter as clinically indicated. Dose escalations over 20 mg in CYP 2C19 poor metabolizers or patients taking concomitant cimetidine is not recommended.

Individually corrected QTc (QTcNi) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 119 healthy subjects. The maximum mean (90% upper confidence interval) difference from placebo arm were 8.5 (10.8) and 18.5 (21.0) ms for 20-mg and 60-mg citalopram, respectively. Based on the established exposure-response relationship, the predicted QTcNi change from placebo arm (90% upper confidence interval) under the C_{max} for the dose of 40 mg is 12.6 (14.3) ms. Citalopram 60-mg dose only represents the therapeutic exposure in patients who are not CYP2C19 poor metabolizer or not taking concomitant cimetidine. Exposure following 60 mg/day is adequate to cover exposure expected after 40 mg /day in a CYP2C19 poor metabolizer or a patient on concomitant cimetidine.

● Section 6 ADVERSE REACTIONS/ ECG Changes subsection

In a through QT study, Celexa was found to be associated with a ^(b)₍₄₎ increase in the QTc interval [see Warnings ^(b)₍₄₎].

Electrocardiograms from Celexa (N=802) and placebo (N=241) 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. A statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. ~~There were no observed differences in QT or other ECG intervals.~~



Recommendation:

We recommend that for the clinical trials, you report outlier data (subjects with QTc changes over 60 ms from baseline or absolute values over 500 ms post-dose) and tachycardic or

bradycardic outliers (increase to over 100 bpm or decrease to less than 50 bpm with a 25% change from baseline) rather than mean effects.

- **Section 7-Drug Interactions**

7.1 Drugs that prolong the QT interval

ECG monitoring is recommended with concomitant medications that prolong the QT interval. (see Warning and Precautions)

OTHER

Please incorporate the QT prolongation information in your Med Guide response.

We believe that these labeling revisions warrant the issuance of a letter communicating this important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter). We request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

Your submission should also include which healthcare professionals will be receiving this letter and an approximate number of copies which will be disseminated.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA’s “Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants”, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

If you have any questions, email CDR Bill Bender, Senior Regulatory Project Manager, at William.Bender@fda.hhs.gov.

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/

THOMAS P LAUGHREN
12/29/2010



NDA's 021-323/S-033, 021-365/S-024, 020-822/S-038, 021-046/S-016

COMPLETE RESPONSE

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

Dear Ms. Raposo:

We acknowledge receipt of the following Supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA).

- NDA 21-323/S-033, dated April 1, 2010 and received April 2, 2010, for Lexapro (escitalopram oxalate) 5mg, 10mg, and 20mg Tablets
- NDA 21-365/S-024, dated April 1, 2010 and received April 2, 2010, for Lexapro (escitalopram oxalate) 5mg/5mL Solution
- NDA 20-822/S-038, dated April 1, 2010 and received April 2, 2010, for Celexa (citalopram hydrobromide) 10mg, 20mg, and 40mg Tablets
- NDA 21-046/S-016, dated April 1, 2010 and received April 2, 2010, Celexa (citalopram hydrobromide) 10mg/5mL Solution

Reference is also made to Agency communications dated March 15, 2010, and March 23, 2010, requesting the comprehensive Medication Guide for all current generation drugs indicated to treat Major Depressive Disorder (MDD).

These "Prior Approval" labeling supplemental new drug applications provide for a comprehensive medication guide as requested by the Agency.

We have completed the review of your applications and have determined that we cannot approve these applications in their present form.

Based on the submissions we received from the sponsors of current generation antidepressants, we have updated the comprehensive medication guide template. To facilitate the review and to maintain consistency across the drug class, we are asking you to revise and resubmit your Medication Guide using the attached template. Please individualize the template only for drug name, manufacturing/storage information, and where indicated by highlights.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

If you have any questions, email your Regulatory Project Manager at Juliette.Toure@fda.hhs.gov.

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

ENCLOSURE: Comprehensive Medication Guide Template

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

THOMAS P LAUGHREN
09/24/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020822Orig1s038, s040

021046Orig1s016, s017

LABELING

Celexa®
(citalopram hydrobromide)
Tablets/Oral Solution

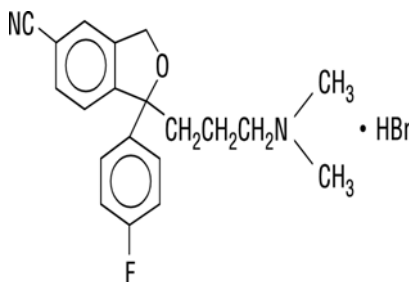
Rx Only

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 Celexa 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. Celexa is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

Celexa® (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram HBr is a racemic bicyclic phthalane derivative designated (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr with the following structural formula:



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

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

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

Celexa 10 mg tablets are film-coated, oval tablets containing citalopram HBr in strengths equivalent to 10 mg citalopram base. Celexa 20 mg and 40 mg tablets are film-coated, oval, scored tablets containing citalopram HBr in strengths equivalent to 20 mg or 40 mg citalopram base. The tablets also contain the following inactive ingredients: copolyvidone, corn starch, crosscarmellose sodium, glycerin, lactose monohydrate, magnesium stearate, hypromellose, microcrystalline cellulose, polyethylene glycol, and titanium dioxide. Iron oxides are used as coloring agents in the beige (10 mg) and pink (20 mg) tablets.

Celexa oral solution contains citalopram HBr equivalent to 2 mg/mL citalopram base. It also contains the following inactive ingredients: sorbitol, purified water, propylene glycol, methylparaben, natural peppermint flavor, and propylparaben.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of citalopram HBr as an antidepressant 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). *In vitro* and *in vivo* studies in animals suggest that citalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long-term (14-day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer.

Citalopram has no or very low affinity for 5-HT_{1A}, 5-HT_{2A}, dopamine D₁ and D₂, α_1 -, α_2 -, and β -adrenergic, histamine H₁, gamma aminobutyric acid (GABA), muscarinic cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of other psychotropic drugs.

Pharmacokinetics

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

concentrations observed after a single dose. The tablet and oral solution dosage forms of citalopram HBr are bioequivalent.

Absorption and Distribution

Following a single oral dose (40 mg tablet) of citalopram, peak blood levels occur at about 4 hours. The absolute bioavailability of citalopram was about 80% relative to an intravenous dose, and absorption is not affected by food. The volume of distribution of citalopram is about 12 L/kg and the binding of citalopram (CT), demethylcitalopram (DCT) and didemethylcitalopram (DDCT) to human plasma proteins is about 80%.

Metabolism and Elimination

Following intravenous administrations of citalopram, the fraction of drug recovered in the urine as citalopram and DCT was about 10% and 5%, respectively. The systemic clearance of citalopram was 330 mL/min, with approximately 20% of that due to renal clearance.

Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide, and a deaminated propionic acid derivative. In humans, unchanged citalopram is the predominant compound in plasma. 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 vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram.

Population Subgroups

Age - Citalopram pharmacokinetics in subjects ≥ 60 years of age were compared to younger subjects in two normal volunteer studies. In a single-dose study, citalopram AUC and half-life were increased in the elderly subjects by 30% and 50%, respectively, whereas in a multiple-dose study they were increased by 23% and 30%, respectively. 20 mg is the recommended dose for most elderly patients (see **DOSAGE AND ADMINISTRATION**). 20 mg/day is the maximum recommended dose for those who are CYP2C19 poor metabolizers or who are also taking a CYP2C19 inhibitor such as cimetidine, due to the risk of QT prolongation.

Gender - In three pharmacokinetic studies (total N=32), citalopram AUC in women was one and a half to two times that in men. This difference was not observed in five other pharmacokinetic studies (total N=114). In clinical studies, no differences in steady state serum citalopram levels were seen between men (N=237) and women (N=388). There were no gender differences in the pharmacokinetics of DCT and DDCT. No adjustment of dosage on the basis of gender is

recommended.

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. 20 mg is the recommended dose for most hepatically impaired patients (see **DOSAGE AND ADMINISTRATION**).

Reduced renal function - In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of citalopram 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 citalopram on CYP3A4, -2C9, or -2E1, but did suggest that it is a weak inhibitor of CYP1A2, -2D6, and -2C19.

Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. However, *in vivo* data to address this question are limited.

Since CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of 3A4 (e.g., ketoconazole, itraconazole, and macrolide antibiotics) and potent inhibitors of CYP2C19 (e.g., omeprazole) might decrease the clearance of citalopram. However, coadministration of citalopram and the potent 3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple-dose administration of Celexa, suggesting that coadministration, with Celexa, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on citalopram metabolism. See **Drug Interactions** under **PRECAUTIONS** for more detailed information on available drug interaction data. Celexa 20 mg/day is the maximum recommended dose for patients taking concomitant cimetidine or another CYP2C19 inhibitor because of the risk of QT prolongation.

Clinical Efficacy Trials

The efficacy of Celexa as a treatment for depression was established in two placebo-controlled studies (of 4 to 6 weeks in duration) in adult outpatients (ages 18-66) meeting DSM-III or DSM-III-R criteria for major depression. Study 1, a 6-week trial in which patients received fixed Celexa doses of 10, 20, 40, and 60 mg/day, showed that Celexa at doses of 40 and 60 mg/day was effective as measured by the Hamilton Depression Rating Scale (HAMD) total score, the HAMD depressed mood item (Item 1), the Montgomery Asberg Depression Rating Scale, and

the Clinical Global Impression (CGI) Severity scale. This study showed no clear effect of the 10 and 20 mg/day doses, and the 60 mg/day dose was not more effective than the 40 mg/day dose. In study 2, a 4-week, placebo-controlled trial in depressed patients, of whom 85% met criteria for melancholia, the initial dose was 20 mg/day, followed by titration to the maximum tolerated dose or a maximum dose of 80 mg/day. Patients treated with Celexa showed significantly greater improvement than placebo patients on the HAMD total score, HAMD item 1, and the CGI Severity score. In three additional placebo-controlled depression trials, the difference in response to treatment between patients receiving Celexa and patients receiving placebo was not statistically significant, possibly due to high spontaneous response rate, smaller sample size, or, in the case of one study, too low a dose.

In two long-term studies, depressed patients who had responded to Celexa during an initial 6 or 8 weeks of acute treatment (fixed doses of 20 or 40 mg/day in one study and flexible doses of 20-60 mg/day in the second study) were randomized to continuation of Celexa or to placebo. In both studies, patients receiving continued Celexa treatment experienced significantly lower relapse rates over the subsequent 6 months compared to those receiving placebo. In the fixed-dose study, the decreased rate of depression relapse was similar in patients receiving 20 or 40 mg/day of Celexa.

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.

Comparison of Clinical Trial Results

Highly variable results have been seen in the clinical development of all antidepressant drugs. Furthermore, in those circumstances when the drugs have not been studied in the same controlled clinical trial(s), comparisons among the results of studies evaluating the effectiveness of different antidepressant drug products are inherently unreliable. Because conditions of testing (e.g., patient samples, investigators, doses of the treatments administered and compared, outcome measures, etc.) vary among trials, it is virtually impossible to distinguish a difference in drug effect from a difference due to one of the confounding factors just enumerated.

INDICATIONS AND USAGE

Celexa (citalopram HBr) is indicated for the treatment of depression.

The efficacy of Celexa in the treatment of depression was established in 4-6 week, controlled trials of outpatients whose diagnosis corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder (see **CLINICAL PHARMACOLOGY**).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily

functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. The antidepressant action of Celexa in hospitalized depressed patients has not been adequately studied.

The efficacy of Celexa in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials (see **CLINICAL PHARMACOLOGY**). Nevertheless, the physician who elects to use Celexa for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

Celexa is contraindicated in patients with congenital long QT syndrome (see **WARNINGS**, **PRECAUTIONS**, and **Drug Interactions**).

Concomitant use in patients taking pimozide is contraindicated (see **PRECAUTIONS**).

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

WARNINGS

WARNINGS-Clinical Worsening and Suicide Risk

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 **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with Celexa**, for a description of the risks of discontinuation of Celexa).

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

QT-Prolongation and Torsade de Pointes

Citalopram causes dose-dependent QT prolongation and should not be dosed above 40 mg/day. Torsade de Pointes has been reported postmarketing. Celexa should not be used in patients with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalations over 20 mg/day in CYP2C19 poor metabolizers or patients taking concomitant cimetidine or another CYP2C19 inhibitor are not recommended.

Individually corrected QTc (QTcNi) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 119 healthy

subjects. The maximum mean (upper bound of the 95% one-sided confidence interval) difference from placebo were 8.5 (10.8) and 18.5 (21.0) msec for 20 mg and 60 mg citalopram, respectively. Based on the established exposure-response relationship, the predicted QTcNi change from placebo (upper bound of the 95% one-sided confidence interval) under the C_{max} for the dose of 40 mg is 12.6 (14.3) msec. In those patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, higher citalopram exposure would be expected, along with any concomitant risks.

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 Celexa is not approved for use in treating bipolar depression.

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 Celexa 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 Celexa before starting an MAOI.

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 Celexa 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 Celexa with MAOIs intended to treat depression is contraindicated. If concomitant treatment of Celexa 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 Celexa with serotonin precursors (such as tryptophan) is not recommended. Treatment with Celexa 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.

PRECAUTIONS

General

Discontinuation of Treatment with Celexa

During marketing of Celexa 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 Celexa. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION**).

Abnormal Bleeding

SSRIs and SNRIs, including Celexa, 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 Celexa and NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Celexa. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Celexa 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**). Discontinuation of Celexa 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.

Activation of Mania/Hypomania

In placebo-controlled trials of Celexa, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with Celexa and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants. As with all antidepressants, Celexa should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of citalopram have been observed in animal studies, Celexa 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 Celexa, seizures occurred in 0.3% of patients treated with Celexa (a rate of one patient per 98 years of exposure) and 0.5% of patients treated with placebo (a rate of one patient per 50 years of exposure). Like other antidepressants, Celexa should be introduced with care in patients with a history of seizure disorder.

Interference with Cognitive and Motor Performance

In studies in normal volunteers, Celexa in doses of 40 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities.

Use in Patients with Concomitant Illness

Clinical experience with Celexa in patients with certain concomitant systemic illnesses is limited. Due to the risk of QT prolongation, ECG monitoring is advised when using Celexa in patients with congestive heart failure, bradyarrhythmias, or who are taking medications that prolong the QT interval. Caution is advised in treating patients with diseases or conditions that cause hypokalemia or hypomagnesemia.

Celexa 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. However, the electrocardiograms of 1116 patients who received Celexa in clinical trials were evaluated and the data indicate that Celexa is not associated with the development of clinically significant ECG abnormalities.

In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Celexa in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (see **DOSAGE AND ADMINISTRATION**).

Because citalopram 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 Celexa, however, it should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

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

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of **Celexa** and triptans, tramadol or other serotonergic agents.

Although in controlled studies Celexa has not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking, or motor skills, so patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably

certain that Celexa therapy does not affect their ability to engage in such activities.

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

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

Patients should be cautioned about the concomitant use of Celexa 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.

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

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

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

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Celexa 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 Celexa. 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 Celexa.

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.

Laboratory Tests

There are no specific laboratory tests recommended.

QT-Prolongation and Torsade de Pointes

Citalopram causes dose dependent QT prolongation and should not be dosed above 40 mg/day. Torsade de Pointes has been reported postmarketing. Celexa should not be used in patients with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalations over 20 mg/day in CYP2C19 poor metabolizers or patients taking concomitant cimetidine or another CYP2C19 inhibitor are not recommended.

Drug Interactions

Drugs that Prolong the QT interval: ECG monitoring is recommended with concomitant medications that have demonstrated prolongation of the QT interval (see **WARNINGS- QT-Prolongation and Torsade de Pointes**).

Serotonergic Drugs: Based on the mechanism of action of SNRIs and SSRIs including Celexa, and the potential for serotonin syndrome, caution is advised when Celexa 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-Serotonin Syndrome**). The concomitant use of **Celexa** with other SSRIs, SNRIs or tryptophan is not recommended (see **PRECAUTIONS - Drug Interactions**).

Triptans: There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Celexa with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS - Serotonin Syndrome**).

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

Alcohol - Although citalopram did not potentiate the cognitive and motor effects of alcohol in a

clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking Celexa is not recommended.

Monoamine Oxidase Inhibitors (MAOIs) - See **CONTRAINDICATIONS** and **WARNINGS**.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.) - Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin 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 Celexa is initiated or discontinued.

Cimetidine - In subjects who had received 21 days of 40 mg/day Celexa, 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.

Celexa 20 mg/day is the maximum recommended dose for patients taking concomitant cimetidine because of the risk of QT prolongation (see **DOSAGE AND ADMINISTRATION**).

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

Lithium - Coadministration of Celexa (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 citalopram, caution should be exercised when Celexa and lithium are coadministered.

Pimozide - In a controlled study, a single dose of pimozide 2 mg co-administered with 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. Citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

Theophylline - Combined administration of Celexa (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.

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

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

Carbamazepine - Combined administration of Celexa (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 citalopram should be considered if the two drugs are coadministered.

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

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

CYP3A4 and 2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance.

Celexa 20 mg/day is the maximum recommended dose for patients taking concomitant CYP2C19 inhibitors because of the risk of QT prolongation (see **DOSAGE AND ADMINISTRATION**).

Metoprolol - Administration of 40 mg/day Celexa for 22 days resulted in a two-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Celexa and metoprolol had no clinically significant effects on blood pressure or heart rate.

Imipramine and Other Tricyclic Antidepressants (TCAs) - *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of Celexa (40 mg/day for 10 days) with the TCA imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCAs with Celexa.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 citalopram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended human daily dose (MRHD) of 60 mg on a surface area (mg/m^2) basis. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, respectively, on a mg/m^2 basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

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. 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 citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses \geq 32 mg/kg/day, approximately 5 times the MRHD of 60 mg/day on a body surface area (mg/m^2) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.

Pregnancy

Pregnancy Category C

In animal reproduction studies, 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 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, which is approximately 18 times the MRHD of 60 mg/day on a body surface area (mg/m^2) basis. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental, no-effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m^2 basis. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of up to 16 mg/kg/day, or approximately 5 times the MRHD on a mg/m^2 basis. Thus, teratogenic effects were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with 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, which is approximately 5 times the MRHD on a mg/m^2 basis. The no-effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m^2 basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses \square 24 mg/kg/day, approximately 4 times the MRHD on a mg/m^2 basis. A no-effect dose was not determined in that study.

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

Pregnancy-Nonteratogenic Effects

Neonates exposed to Celexa 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**).

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 Celexa during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**). 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.

Labor and Delivery

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

Nursing Mothers

As has been found to occur with many other drugs, citalopram is excreted in human breast milk. There have been 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. The decision whether to continue or discontinue either nursing or Celexa therapy should take into account the risks of citalopram exposure for the infant and the benefits of Celexa treatment for the mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see **BOXED WARNING and WARNINGS—Clinical Worsening and Suicide Risk**). Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with Celexa, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Celexa in a child or adolescent must balance the potential risks with the clinical need.

Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and

adolescents treated with Celexa.

Geriatric Use

Of 4422 patients in clinical studies of Celexa, 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 greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with Celexa in clinical trials received daily doses between 20 and 40 mg (see **DOSAGE AND ADMINISTRATION**).

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

In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively (see **CLINICAL PHARMACOLOGY**).

20 mg/day is the recommended dose for most elderly patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for Celexa included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient-exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Celexa varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials

Adverse Events Associated with Discontinuation of Treatment

Among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (i.e., associated with discontinuation in at least 1% of Celexa-treated patients at a rate at least twice that of placebo) are shown in **TABLE 2**. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in this table.

TABLE 2

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled, Depression Trials		
	Percentage of Patients Discontinuing	
	Due to Adverse Event	
	Citalopram	Placebo
	(N=1063)	(N=446)
Body System/Adverse Event		
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomiting	1%	0%
Central and Peripheral		
Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Adverse Events Occurring at an Incidence of 2% or More Among Celexa-Treated Patients

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with Celexa and for which the incidence in patients treated with Celexa was greater than the incidence in placebo-treated patients.

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

The only commonly observed adverse event that occurred in Celexa patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see **TABLE 3**).

TABLE 3

Treatment-Emergent Adverse Events:		
Incidence in Placebo-Controlled Clinical Trials*		
(Percentage of Patients Reporting Event)		
Body System/Adverse Event	Celexa (N=1063)	Placebo (N=446)
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central & Peripheral Nervous System Disorders		
Tremor	8%	6%
Gastrointestinal Disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%

Vomiting	4%	3%
Abdominal Pain	3%	2%
General		
Fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea ¹	3%	2%
Libido Decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation Disorder ^{2,3}	6%	1%
Impotence ³	3%	<1%

*Events reported by at least 2% of patients treated with Celexa are reported, except for the following events which had an incidence on placebo \geq Celexa: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.

¹Denominator used was for females only (N=638 Celexa; N=252 placebo).

²Primarily ejaculatory delay.

³Denominator used was for males only (N=425 Celexa; N=194 placebo).

Dose Dependency of Adverse Events

The potential relationship between the dose of Celexa administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or Celexa 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response ($p < 0.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning.

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.

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

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

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

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

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Celexa 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 Celexa treatment. In addition, a comparison of supine and standing vital sign measures for Celexa and placebo treatments indicated that Celexa treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with Celexa in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients.

Laboratory Changes

Celexa 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 Celexa treatment.

ECG Changes

In a thorough QT study, Celexa was found to be associated with a dose-dependent increase in the QTc interval (see **WARNINGS - QT-Prolongation and Torsade de Pointes**).

Electrocardiograms from Celexa (N=802) and placebo (N=241) groups were compared with respect to outliers defined as subjects with QTc changes over 60 msec from baseline or absolute values over 500 msec post-dose, and subjects with heart rate increases to over 100 bpm or decreases to less than 50 bpm with a 25% change from baseline (tachycardic or bradycardic outliers, respectively). In the Celexa group 1.9% of the patients had a change from baseline in QTcF >60 msec compared to 1.2% of the patients in the placebo group. None of the patients in the placebo group had a post-dose QTcF >500 msec compared to 0.5% of the patients in the Celexa group. The incidence of tachycardic outliers was 0.5% in the Celexa group and 0.4% in the placebo group. The incidence of bradycardic outliers was 0.9% in the Celexa group and 0.4% in the placebo group.

Other Events Observed During the Premarketing Evaluation of Celexa (citalopram HBr)

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by patients treated with Celexa at multiple doses in a range of 10 to 80 mg/day during any phase of a trial within the premarketing database of 4422 patients. All reported events are included except those already listed in **Table 3** or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasize that, although the events reported occurred during treatment

with Celexa, they were not necessarily caused by it.

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

Cardiovascular - *Frequent*: tachycardia, postural hypotension, hypotension. *Infrequent*: hypertension, bradycardia, edema (extremities), angina pectoris, extrasystoles, cardiac failure, flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. *Rare*: transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block.

Central and Peripheral Nervous System Disorders - *Frequent*: paresthesia, migraine. *Infrequent*: hyperkinesia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. *Rare*: abnormal coordination, hyperesthesia, ptosis, stupor.

Endocrine Disorders - *Rare*: hypothyroidism, goiter, gynecomastia.

Gastrointestinal Disorders - *Frequent*: saliva increased, flatulence. *Infrequent*: gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. *Rare*: colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups.

General - *Infrequent*: hot flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms. *Rare*: hay fever.

Hemic and Lymphatic Disorders - *Infrequent*: purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. *Rare*: pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding.

Metabolic and Nutritional Disorders - *Frequent*: decreased weight, increased weight. *Infrequent*: increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. *Rare*: bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration.

Musculoskeletal System Disorders - *Infrequent*: arthritis, muscle weakness, skeletal pain. *Rare*: bursitis, osteoporosis.

Psychiatric Disorders - *Frequent*: impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. *Infrequent*: increased libido, aggressive reaction, paroniria, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. *Rare*: catatonic reaction, melancholia.

Reproductive Disorders/Female* - *Frequent*: amenorrhea. *Infrequent*: galactorrhea, breast pain, breast enlargement, vaginal hemorrhage.

*% based on female subjects only: 2955

Respiratory System Disorders - *Frequent*: coughing. *Infrequent*: bronchitis, dyspnea, pneumonia. *Rare*: asthma, laryngitis, bronchospasm, pneumonitis, sputum increased.

Skin and Appendages Disorders - *Frequent*: rash, pruritus. *Infrequent*: photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. *Rare*: hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani.

Special Senses - *Frequent*: accommodation abnormal, taste perversion. *Infrequent*: tinnitus, conjunctivitis, eye pain. *Rare*: mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss.

Urinary System Disorders - *Frequent*: polyuria. *Infrequent*: micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare*: facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain.

Other Events Observed During the Postmarketing Evaluation of Celexa (citalopram HBr)

It is estimated that over 30 million patients have been treated with Celexa since market introduction. Although no causal relationship to Celexa treatment has been found, the following adverse events have been reported to be temporally associated with Celexa treatment, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, glaucoma, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, ventricular arrhythmia, torsade de pointes, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Celexa (citalopram HBr) is not a controlled substance.

Physical and Psychological Dependence

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

OVERDOSAGE

Human Experience

In clinical trials of citalopram, there were reports of citalopram overdose, including overdoses of up to 2000mg, with no associated fatalities. During the postmarketing evaluation of citalopram, Celexa overdoses, including overdoses of up to 6000 mg, have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely reported.

Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, and sinus tachycardia. In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

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 citalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Celexa.

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

DOSAGE AND ADMINISTRATION

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

Initial Treatment

Celexa (citalopram HBr) should be administered at an initial dose of 20 mg once daily, with an increase to a maximum dose of 40 mg/day. Dose increase should usually occur in increments of 20 mg at intervals of no less than one week. Doses above 40 mg/day are not recommended due to the risk of QT prolongation. Additionally, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose.

Special Populations

20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients. 20 mg/day is the maximum recommended dose for CYP2C19 poor metabolizers or those patients taking cimetidine or another CYP2C19 inhibitor.

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

Treatment of Pregnant Women During the Third Trimester

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

Maintenance Treatment

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Systematic evaluation of Celexa in two studies has shown that its antidepressant efficacy is maintained for periods of up to 24 weeks following 6 or 8 weeks of initial treatment (32 weeks total). In one study, patients were assigned randomly to placebo or to the same dose of Celexa (20-60 mg/day) during maintenance treatment as they had received during the acute stabilization phase, while in the other study, patients were assigned randomly to continuation of Celexa 20 or 40 mg/day, or placebo, for maintenance treatment. In the latter study, the rates of relapse to depression were similar for the two dose groups (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**). Based on these limited data, it is not known whether the dose of citalopram needed to maintain euthymia is identical to the dose needed to induce remission. If adverse reactions are bothersome, a decrease in dose to 20 mg/day can be considered.

Discontinuation of Treatment with Celexa

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

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of Celexa therapy. Similarly, at least 14 days should be allowed after stopping Celexa before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED

Tablets:

10 mg	Bottle of 100	NDC # 0456-4010-01
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Beige, oval, film-coated.

Imprint on one side with "FP". Imprint on the other side with "10 mg".

20 mg	Bottle of 100	NDC # 0456-4020-01
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10 x 10 Unit Dose		NDC # 0456-4020-63
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Pink, oval, scored, film-coated.

Imprint on scored side with "F" on the left side and "P" on the right side.

Imprint on the non-scored side with "20 mg".

40 mg	Bottle of 100	NDC # 0456-4040-01
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10 x 10 Unit Dose		NDC # 0456-4040-63
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White, oval, scored, film-coated.

Imprint on scored side with "F" on the left side and "P" on the right side.

Imprint on the non-scored side with "40 mg".

Oral Solution:

10 mg/5 mL, peppermint flavor (240 mL)	NDC# 0456-4130-08
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Store at 25°C (77°F); excursions permitted to 15 - 30°C (59-86°F).

ANIMAL TOXICOLOGY

Retinal Changes in Rats

Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-

year carcinogenicity study with citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day (13 times the maximum recommended daily human dose of 60 mg on a mg/m² basis). Similar findings were not present in rats receiving 24 mg/kg/day for two years, in mice treated for 18 months at doses up to 240 mg/kg/day, or in dogs treated for one year at doses up to 20 mg/kg/day (4, 20, and 10 times, respectively, the maximum recommended daily human dose on a mg/m² basis).

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 doses of 8 mg/kg/day (4 times the maximum recommended daily human dose of 60 mg on a mg/m² basis) died suddenly between weeks 17 and 31 following initiation of treatment. Although appropriate data from that study are not available to directly compare plasma levels of citalopram (CT) and its metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), to levels that have been achieved in humans, pharmacokinetic data indicate that the relative dog-to-human exposure was greater for the metabolites than for citalopram. Sudden deaths were not observed in rats at doses up to 120 mg/kg/day, which produced plasma levels of CT, DCT, and DDCT similar to those observed in dogs at doses of 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs. This effect occurred in dogs at doses producing peak DDCT plasma levels of 810 to 3250 nM (39-155 times the mean steady state DDCT plasma level measured at the maximum recommended human daily dose of 60 mg). In dogs, peak DDCT plasma concentrations are approximately equal to peak CT plasma concentrations, whereas in humans, steady state DDCT plasma concentrations are less than 10% of steady state CT plasma concentrations. Assays of DDCT plasma concentrations in 2020 citalopram-treated individuals demonstrated that DDCT levels rarely exceeded 70 nM; the highest measured level of DDCT in human overdose was 138 nM. While DDCT is ordinarily present in humans at lower levels than in dogs, it is unknown whether there are individuals who may achieve higher DDCT levels. The possibility that DCT, a principal metabolite in humans, may prolong the QT interval in dogs has not been directly examined because DCT is rapidly converted to DDCT in that species.

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

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Medication Guide

Celexa[®] (se-lek-sa)
(citalopram hydrobromide)
Tablets/Oral Solution

Read the Medication Guide that comes with Celexa before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about Celexa?

Celexa and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

- **Celexa and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed**.
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
 - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
 - Pay particular attention to such changes when Celexa is started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. Celexa may be associated with these serious side effects:

2. Changes in the electrical activity of your heart (QT prolongation and Torsade de Pointes).

This condition can be life threatening.
The symptoms may include:

- chest pain
- fast or slow heartbeat
- shortness of breath
- dizziness or fainting

3. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions. This condition can be life-threatening and may include:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle rigidity

4. Severe allergic reactions:

- trouble breathing
- swelling of the face, tongue, eyes or mouth
- rash, itchy welts (hives) or blisters, alone or with fever or joint pain

5. Abnormal bleeding: Celexa and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin[®], Jantoven[®]), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.

6. Seizures or convulsions

7. Manic episodes:

- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior

- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

8. Changes in appetite or weight.

Children and adolescents should have height and weight monitored during treatment.

9. Low salt (sodium) levels in the blood. Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

Do not stop Celexa without first talking to your healthcare provider.

Stopping Celexa too quickly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or changes in sleep habits
- headache, sweating, nausea, dizziness
- electric shock-like sensations, shaking, confusion

What is Celexa?

Celexa is a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider. Celexa is also used to treat:

- Major Depressive Disorder (MDD)

Talk to your healthcare provider if you do not think that your condition is getting better with Celexa treatment.

Who should not take Celexa?

Do not take Celexa if you:

- are allergic to citalopram hydrobromide or escitalopram oxalate or any of the ingredients in Celexa. See the end of this Medication Guide for a complete list of ingredients in Celexa.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
 - Do not take an MAOI within 14 days of stopping Celexa.
 - Do not start Celexa if you stopped taking an MAOI in the last 14 days.

People who take Celexa close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:

- high fever
- uncontrolled muscle spasms
- stiff muscles
- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)
- **take the antipsychotic medicine pimozide (Orap[®]) because this can cause serious heart problems.**
- **have a heart problem including congenital long QT syndrome**

What should I tell my healthcare provider before taking Celexa? Ask if you are not sure.

Before starting Celexa, tell your healthcare provider if you

- Are taking certain drugs such as:
 - Medicines for heart problems

- Medicines that lower your potassium or magnesium levels in your body
- Cimetidine
- Triptans used to treat migraine headache
- Medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, SSRIs, SNRIs, or antipsychotics
- Tramadol
- Over-the-counter supplements such as tryptophan or St. John's Wort

- have liver problems
- have kidney problems
- have heart problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have a history of a stroke
- have high blood pressure
- have or had bleeding problems
- are pregnant or plan to become pregnant. It is not known if Celexa will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy
- are breast-feeding or plan to breast-feed. Some Celexa may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking Celexa.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Celexa and some medicines may interact with each other,

may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take Celexa with your other medicines. Do not start or stop any medicine while taking Celexa without talking to your healthcare provider first.

If you take Celexa, you should not take any other medicines that contain citalopram hydrobromide or escitalopram oxalate including: Lexapro.

How should I take Celexa?

- Take Celexa exactly as prescribed. Your healthcare provider may need to change the dose of Celexa until it is the right dose for you.
- Celexa may be taken with or without food.
- If you miss a dose of Celexa, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of Celexa at the same time.
- If you take too much Celexa, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking Celexa?

Celexa can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how Celexa

affects you. Do not drink alcohol while using Celexa.

What are the possible side effects of Celexa?

Celexa may cause serious side effects, including:

See “What is the most important information I should know about Celexa?”

Common possible side effects in people who take Celexa include:

- Nausea
- Sleepiness
- Weakness
- Dizziness
- Feeling anxious
- Trouble sleeping
- Sexual problems
- Sweating
- Shaking
- Not feeling hungry
- Dry mouth
- Constipation
- Diarrhea
- Respiratory Infections
- Yawning

Other side effects in children and adolescents include:

- increased thirst
- abnormal increase in muscle movement or agitation
- nose bleed
- urinating more often
- heavy menstrual periods
- possible slowed growth rate and weight change. Your child's height and weight should be

monitored during treatment with Celexa.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Celexa. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store Celexa?

- Store Celexa at 25°C (77°F), between 15°C to 30°C (59°F to 86°F).
- Keep Celexa bottle closed tightly.

Keep Celexa and all medicines out of the reach of children.

General information about Celexa

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Celexa for a condition for which it was not prescribed. Do not give Celexa to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about Celexa. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about Celexa that is written for healthcare professionals.

For more information about Celexa call 1-800-678-1605 or go to www.Celexa.com.

What are the ingredients in Celexa?

Active ingredient: citalopram hydrobromide

Inactive ingredients:

- **Tablets:** copolyvidone, corn starch, croscarmellose sodium, glycerin, lactose monohydrate, magnesium stearate, hypromellose, microcrystalline cellulose, polyethylene glycol, titanium dioxide and iron dioxide for coloring.
- **Oral Solution:** sorbitol, purified water, propylene glycol, methylparaben, natural peppermint flavor, and propylparaben.

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

Revised: 08/2011

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/s/

THOMAS P LAUGHREN
08/12/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020822Orig1s038, s040

021046Orig1s016, s017

MEDICAL REVIEW(S)

**Review and Evaluation of Clinical Data
NDA 020822**

Sponsor:	Forest Laboratories, Inc.
Drug:	Celexa
Indications:	Major Depressive Disorder (MDD)
Material Submitted:	SLR-038
Related Supplement:	NDA 021046/SLR-016
DARRTS Letter Date:	November 24, 2010
Date Received:	November 26, 2010
DARRTS SDN:	231

I. Background

In response to the Division's comprehensive Medication Guide (MG) Prior Approval (PA) Complete Response (CR) letter dated September 16, 2010 for NDA 020822/S-038 (Celexa tablet) and NDA 021046/S-016 (Celexa solution), the sponsor Forest submitted their proposed MG for Celexa both tablet and oral solution based on the MG template provided by the Division.

The Division has made revisions in the "CONTRAINDICATIONS", "WARNINGS AND PRECAUTIONS" and "DRUG INTERACTIONS" sections of the label based on the thorough QT study results.

II. Clinical Review of the Proposed Medication Guide

The proposed MG by Forest with my track changes is appended. Most of the revisions made by Forest were acceptable.

III. Conclusions and Recommendations

The sponsor's proposed MG requires further revision before it may be approved.

This reviewer has incorporated the revisions in the "CONTRAINDICATIONS", "WARNINGS AND PRECAUTIONS" and "DRUG INTERACTIONS" sections of the label into the MG. The revised MG is appended in the end of this review.

IV. Comments to the Sponsor

We have reviewed your proposed Medication Guide for Celexa dated November 24, 2010. Most of your revisions to the Medication Guide are acceptable. Some however, need modifications before it can be approved. Please see the attached Medication Guide for details.

Jenn Sellers, M.D., Ph.D., FAAP
May 18, 2011

cc: NDA 021046 and NDA 020822
TLaughren/MMathis/JZhang/GDubitsky/PDavid/WBender

Medication Guide
Celexa® (se-lek-sa)
(citalopram hydrobromide)
Tablets/Oral Solution

Read the Medication Guide that comes with Celexa before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about Celexa?

Celexa and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

• **Celexa and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**

• Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.

• Watch for these changes and call your healthcare provider right away if you notice:

- New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
- Pay particular attention to such changes when Celexa is started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an

emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency.

Celexa may be associated with these serious side effects:

2. QT-Prolongation and Torsade de Pointes. (b) (4)

3. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions. This condition can be life-threatening and may include:

- agitation, hallucinations, coma or other changes in mental status

76	• coordination problems or muscle	122	• anxiety, irritability, high or low mood,
77	twitching (overactive reflexes)	123	feeling restless or changes in sleep habits
78	• racing heartbeat, high or low blood	124	• headache, sweating, nausea, dizziness
79	pressure	125	• electric shock-like sensations, shaking,
80	• sweating or fever	126	confusion
81	• nausea, vomiting, or diarrhea	127	What is Celexa?
82	• muscle rigidity	128	Celexa is a prescription medicine used to
83	34. Severe allergic reactions:	129	treat depression. It is important to talk with
84	• trouble breathing	130	your healthcare provider about the risks of
85	• swelling of the face, tongue, eyes or	131	treating depression and also the risks of not
86	mouth	132	treating it. You should discuss all treatment
87	• rash, itchy welts (hives) or blisters,	133	choices with your healthcare provider.
88	alone or with fever or joint pain	134	Celexa is <u>also</u> used to treat:
89	45. Abnormal bleeding: Celexa and other	135	• Major Depressive Disorder (MDD)
90	antidepressant medicines may increase	136	Talk to your healthcare provider if you do
91	your risk of bleeding or bruising,	137	not think that your condition is getting better
92	especially if you take the blood thinner	138	with Celexa treatment.
93	warfarin (Coumadin [®] , Jantoven [®]), a	139	
94	non-steroidal anti-inflammatory drug	140	Who should not take Celexa?
95	(NSAIDs, like ibuprofen or naproxen),	141	
96	or aspirin.	142	Do not take Celexa if you:
97	56. Seizures or convulsions	143	• are allergic to citalopram hydrobromide
98	67. Manic episodes:	144	or escitalopram oxalate or any of the
99	• greatly increased energy	145	ingredients in Celexa. See the end of this
100	• severe trouble sleeping	146	Medication Guide for a complete list of
101	• racing thoughts	147	ingredients in Celexa.
102	• reckless behavior	148	• take a Monoamine Oxidase Inhibitor
103	• unusually grand ideas	149	(MAOI). Ask your healthcare provider
104	• excessive happiness or irritability	150	or pharmacist if you are not sure if you
105	• talking more or faster than usual	151	take an MAOI, including the antibiotic
106	78. Changes in appetite or weight.	152	linezolid.
107	Children and adolescents should have	153	• Do not take an MAOI within 14 days
108	height and weight monitored during	154	of stopping Celexa.
109	treatment.	155	• Do not start Celexa if you stopped
110	89. Low salt (sodium) levels in the blood.	156	taking an MAOI in the last 14 days
111	Elderly people may be at greater risk for	157	
112	this. Symptoms may include:	158	
113	• headache	159	
114	• weakness or feeling unsteady	160	People who take Celexa close in time
115	• confusion, problems concentrating or	161	to an MAOI may have serious or even
116	thinking or memory problems	162	life-threatening side effects. Get
117		163	medical help right away if you have
118	Do not stop Celexa without first talking to	164	any of these symptoms:
119	your healthcare provider. Stopping Celexa	165	• high fever
120	too quickly may cause serious symptoms	166	• uncontrolled muscle spasms
121	including:		• stiff muscles

(b) (4)

- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)
- **take the antipsychotic medicine pimozone (Orap[®]) because this can cause serious heart problems.**
- **have congenital long QT syndrome**

What should I tell my healthcare provider before taking Celexa? Ask if you are not sure.

Before starting Celexa, tell your healthcare provider if you:

- Are taking certain drugs such as:
 - **Medicines** (b) (4)
 - **Medicines that lower your potassium or magnesium levels in your body**
 - **cimetidine**
 - Triptans used to treat migraine headache
 - Medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, SSRIs, SNRIs, or antipsychotics
 - tramadol
 - Over-the-counter supplements such as tryptophan or St. John's Wort
- have liver problems
- have kidney problems
- have heart problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have a history of a stroke
- have high blood pressure
- have or had bleeding problems
- (b) (4)
- are pregnant or plan to become pregnant. It is not known if Celexa will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy

- are breast-feeding or plan to breast-feed. Some Celexa may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking Celexa.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Celexa and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take Celexa with your other medicines. Do not start or stop any medicine while taking Celexa without talking to your healthcare provider first.

If you take Celexa, you should not take any other medicines that contain citalopram hydrobromide or escitalopram oxalate including: Lexapro.

How should I take Celexa?

- Take Celexa exactly as prescribed. Your healthcare provider may need to change the dose of Celexa until it is the right dose for you.
- Celexa may be taken with or without food.
- If you miss a dose of Celexa, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of Celexa at the same time.
- If you take too much Celexa, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking Celexa?

Celexa can cause sleepiness or may affect your ability to make decisions, think clearly,

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258 or react quickly. You should not drive,
259 operate heavy machinery, or do other
260 dangerous activities until you know how
261 Celexa affects you. Do not drink alcohol
262 while using Celexa.

264 What are the possible side effects of 265 Celexa?

266 **Celexa may cause serious side effects,**
267 **including:** (b) (4)

271 ~~See "What is the most important~~
272 ~~information I should know about Celexa?"~~ (b) (4)

274 Common possible side effects in people who
275 take Celexa include:

276 (b) (4)
277 •sexual problems (b) (4)

278 (b) (4)
279 (b) (4)
280 (b) (4)
281 (b) (4)
282 (b) (4)
283 (b) (4)
284 •yawning (b) (4)

285 (b) (4)
286 (b) (4)
287 •sweating (b) (4)
288 •feeling anxious (b) (4)
289 (b) (4)

- 290 • Nausea
- 291 • Sleepiness
- 292 • Weakness
- 293 • Dizziness
- 294 • Feeling anxious
- 295 • Trouble sleeping
- 296 • Sexual problems
- 297 • Sweating
- 298 • Shaking
- 299 • Not feeling hungry
- 300 • Dry mouth
- 301 • Constipation
- 302 (b) (4)
- 303 • Yawning

304 Other side effects in children and
305 adolescents include:

- 306 • increased thirst
- 307 • abnormal increase in muscle
308 movement or agitation
- 309 • nose bleed
- 310 • urinating more often
- 311 • heavy menstrual periods
- 312 • possible slowed growth rate and
313 weight change. Your child's height
314 and weight should be monitored
315 during treatment with Celexa.

317 Tell your healthcare provider if you have
318 any side effect that bothers you or that does
319 not go away. These are not all the possible
320 side effects of Celexa. For more
321 information, ask your healthcare provider or
322 pharmacist.

323 CALL YOUR DOCTOR FOR 324 MEDICAL ADVICE ABOUT SIDE 325 EFFECTS. YOU MAY REPORT SIDE 326 EFFECTS TO THE FDA AT 1-800-FDA- 327 1088.

328 How should I store Celexa?

- 329 • Store Celexa at 25°C (77°F), between
330 15°C to 30°C (59°F to 86°F).
- 331 • Keep Celexa bottle closed tightly.

332 Keep Celexa and all medicines out of the 333 reach of children.

334 General information about Celexa

335 Medicines are sometimes prescribed for
336 purposes other than those listed in a
337 Medication Guide. Do not use Celexa for a
338 condition for which it was not prescribed.
339 Do not give Celexa to other people, even if
340 they have the same condition. It may harm
341 them.

342 This Medication Guide summarizes the most
343 important information about Celexa. If you
344 would like more information, talk with your
345 healthcare provider. You may ask your
346 healthcare provider or pharmacist for
347 information about Celexa that is written for
348 healthcare professionals.

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349 For more information about Celexa call
350 1-800-678-1605 or go to www.Celexa.com.
351

352 **What are the ingredients in Celexa?**
353

354 Active ingredient: citalopram hydrobromide

355 Inactive ingredients:

356 • **Tablets:** copolyvidone, corn starch,
357 crosscarmellose sodium, glycerin,
358 lactose monohydrate, magnesium
359 stearate, hypromellose,
360 microcrystalline cellulose,
361 polyethylene glycol, titanium dioxide
362 and iron dioxide for coloring.

363 • **Oral Solution:** sorbitol, purified
364 water, propylene glycol,
365 methylparaben, natural peppermint
366 flavor, and propylparaben.
367

368 Forest Pharmaceuticals, Inc.

369 Subsidiary of Forest Laboratories, Inc.

370 St. Louis, MO 63045 USA

371 Revised: ~~MM/YYYY November 2010~~

372 This Medication Guide has been approved
373 by the U.S. Food and Drug Administration.
374

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/s/

JENN W SELLERS
05/19/2011

JING ZHANG
05/19/2011

**Review and Evaluation of Clinical Data
NDA -020822**

Sponsor:	Forest Laboratories, Inc.
Drug:	Celexa
Material Submitted:	SLR 040
Correspondence Date:	March 31, 2010
Date Received:	April 1, 2010
Related Supplement:	NDA 21046/SLR-017

I. Background

Citalopram (Celexa), a selective serotonin reuptake inhibitor (SSRI), was approved for the treatment of Major Depressive Disorder (MDD) in adults and adolescents (aged 12-17) and for Generalized Anxiety Disorder (GAD) in adults.

A clinical pharmacology study examining a potential drug-drug interaction between pimozide and citalopram suggested a QT prolonging effect of citalopram of about 10 msec. The signal was further strengthened by some post-marketing reports that suggested an additive effect of citalopram in patients who may be at risk of QT prolongation. Therefore, DPP requested the sponsor to conduct a thorough QT study for citalopram.

Forest, conducted the Study CIT-PK-15 titled "Evaluation of the Effects of Sequential Multiple-Dose Regimens of Citalopram on Cardiac Repolarization in Healthy Subjects" to investigate the effects of 20mg - 60 mg/day of citalopram on cardiac repolarization. On July 13, 2010, Forest submitted the full clinical report of the study. They concluded that at the recommended therapeutic dosage of 20 mg/day, citalopram was not associated with a clinically significant QTcNi prolongation.

This submission dated April 1, 2010, NDA 020822/040, provides for a Prior Approval Labeling Supplement for Celexa (citalopram Oxalate) oral tablets (10mg, 20mg and 40mg) and oral solution (10mg/5 ml). The sponsor proposed ECG labeling language under **Section 6 ADVERSE REACTIONS /ECG Changes subsection** of the PLR/PI for Celexa according to the results of Study CIT-PK-15.

The Division consulted FDA QT IRT team for the review of the full clinical report of the Study CIT-PK-15 on July 28, 2010.

II. Review of Proposed Labeling

The sponsor added the text regarding the ECG changes in **6. ADVERSE REACTIONS /ECG Changes** as shown in the following paragraph ([the blue underlined is the addition](#)):

6. ADVERSE REACTIONS

6.4 Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials

ECG Changes

Electrocardiograms from Celexa (N=802) and placebo (N=241) 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. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals.

In a double-blind, placebo-controlled, randomized thorough QTc study in healthy subjects (N=119) at the recommended dose of 20mg, citalopram was not associated with a significant QTc prolongation (largest placebo-corrected mean increase in individually corrected QT interval [QTcNi] of 7.72 msec; 2-sided 90% CI, 6.08 – 9.37msec). At the supratherapeutic dose of 60 mg, citalopram had a largest placebo-corrected mean QTcNi interval increase of 17.71 msec (2-sided 90% CI, 16.00 – 19.42 msec). None of the subjects at either the 20 or 60 mg daily dose had a QTcNi interval >480 msec or a prolongation >60 msec.

III. Comments and Recommendations of the QT-IRT

The following is the summary of QT-IRT's findings:

The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound of $\Delta\Delta$ QTcNi for Citalopram (20 mg/d and 60 mg/d) and the Largest Lower Bound for Moxifloxacin (FDA Analysis) Treatment Time

Treatment	Time (hour)	$\Delta\Delta$ QTcNi (ms)	90% CI (ms)
Citalopram 20 mg/d (on Day 9)	4	8.5	(6.2, 10.8)
Moxifloxacin 400 mg (on Day 9)	4	12.2	(9.9, 14.5)*
Citalopram 60 mg/d (on Day 22)	4	18.5	(16.0, 21.0)
Moxifloxacin 400 mg (on Day 22)	4	13.4	(10.9, 15.9)*
Citalopram 40 mg /d [#]	-	12.6	(10.9,14.3) [#]

*Multiple endpoint adjustment was not applied. The largest lower bounds after Bonferroni adjustment for 4 time points for moxifloxacin on Days 9 and 22 are 9.1 ms and 10.0 ms, respectively.

[#] Model predictions based on the concentration-QTc relationship

The following are the recommendations for labeling changes from the QT-IRT:

(1). Deleting some of the original language in the labeling (~~deletion is shown as red strike through~~):

“Electrocardiograms from Celexa (N=802) and placebo (N=241) 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. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. ~~There were no observed differences in QT or other ECG intervals.~~”

(Comments: The sponsor should only report outlier data i.e. QTcF over 500 ms from the clinical trials).

Individually corrected QTc (QTcNi) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 119 healthy subjects. The maximum mean (95% upper confidence bound) difference from placebo arm were 8.5 (10.8) and 18.5 (21.0) ms for 20-mg and supratherapeutic 60-mg citalopram, respectively. Based on the established exposure-response relationship, the predicted QTcNi change from placebo arm (95% upper confidence interval) under the C_{max} for the dose of 40 mg is 12.6 (14.3) ms. Citalopram 60-mg dose only represents the therapeutic exposure in patients who are not CYP2C19 poor metabolizer or take concomitant cimetidine. Considering a 40-mg dose which is most commonly used in clinical practice, exposure following 60 mg/day is adequate to cover exposure expected after 40 mg /day in a CYP2C19 poor metabolizer or a patient with concomitant cimetidine.

[QT team agree to remove the sentence “Considering a 40-mg dose which is most commonly used in clinical practice,”

(2). Adding the following language to the labeling:

Warning and Precautions

QT- Prolongation and Torsade de Pointes

Citalopram causes dose dependent QT prolongation. Torsade de Pointes has been reported post-marketing. Avoid in patients with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalation from 40 mg to 60 mg should be initiated with ECG monitoring in all patients and considered only in the absence of therapeutic alternatives. Dose escalations over 20 mg in CYP2C19 PM or patients taking concomitant cimetidine is not recommended.

IV. Conclusions

DPP internal meetings were held on November 2, 2010 and December 8, 2010 together with the presence of QT-IRT reviewers. The conclusions were summarized as follows:

We cannot approve the labeling applications in their present form.

Instead of incorporating the ECG changes in the “ADVERSE REACTIONS” section of the label, the ECG information need to be included in the “CONTRAINDICATIONS”, “WARNINGS AND PRECAUTIONS” and “DRUG INTERACTIONS” sections of the label. We have used ~~red strike through font for sections to be deleted~~ and blue font underlined for the addition.

- **Section 4 CONTRAINDICATIONS**

- 4.2 QT prolongation**

Celexa is contraindicated in patients with congenital long QT syndrome

- **Section 5 WARNING AND PRECAUTIONS**

- 5.2 QT-prolongation and Torsade de Pointes**

Citalopram causes dose dependent QT prolongation. Torsade de Pointes has been reported postmarketing. Avoid in patients with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalation from 40 mg to 60 mg should be initiated with ECG monitoring in all patients and considered only in the absence of therapeutic alternatives. ECGs should be collected at baseline and periodically thereafter as clinically indicated. Dose escalations over 20 mg in CYP 2C19 poor metabolizers or patients taking concomitant cimetidine is not recommended.

Individually corrected QTc (QTcNi) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 119 healthy subjects. The maximum mean (90% upper confidence interval) difference from placebo arm were 8.5 (10.8) and 18.5 (21.0) ms for 20-mg and 60-mg citalopram, respectively. Based on the established exposure-response relationship, the predicted QTcNi change from placebo arm (90% upper confidence interval) under the Cmax for the dose of 40 mg is 12.6 (14.3) ms. Citalopram 60- mg dose only represents the therapeutic exposure in patients who are not CYP2C19 poor metabolizer or not taking concomitant cimetidine. Exposure following 60 mg/day is adequate to cover exposure expected after 40 mg /day in a CYP2C19 poor metabolizer or a patient on concomitant cimetidine.

- **Section 6 ADVERSE REACTIONS/ ECG Changes subsection**

In a through QT study, Celexa was found to be associated with an increase in the QTc interval [see Warnings and Precautions (5.2)].

Electrocardiograms from Celexa (N=802) and placebo (N=241) 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. A statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. ~~There were no observed differences in QT or other ECG intervals.~~

(b) (4)



Recommendation:

We recommend that for the clinical trials, you report outlier data (subjects with QTc changes over 60 ms from baseline or absolute values over 500 ms post-dose) and tachycardic or bradycardic outliers (increase to over 100 bpm or decrease to less than 50 bpm with a 25% change from baseline) rather than mean effects.

• Section 7-Drug Interactions

7.1 Drugs that prolong the QT interval

ECG monitoring is recommended with concomitant medications that prolong the QT interval. (see Warning and Precautions)

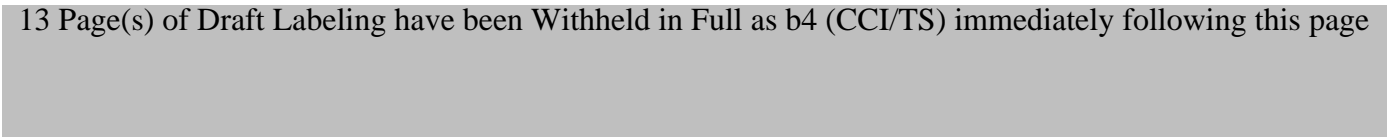
OTHER

Please incorporate the QT prolongation information in your Med Guide response.

Jenn Sellers, M.D., Ph.D., FAAP
December 29, 2010

cc: NDA 021323 and NDA 021365
TLaughren/MMathis/JZhang/GDubitsky/PDavid/WBender

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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/s/

JENN W SELLERS
01/03/2011

JING ZHANG
01/03/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020822Orig1s038, s040

021046Orig1s016, s017

OTHER REVIEW(S)

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Date: August 11, 2011

DRUG/NDA: Celexa (citalopram hydrobromide) 10 mg, 20 mg, and 40 mg Tablets (NDA 020822) and Celexa (citalopram hydrobromide) 10 mg/5 ml Oral Solution (NDA 021046)

Sponsor: Forest Laboratories, Inc.

Indication: Major Depressive Disorder

NDA	Supplement	Dated	Supplement Type	Action
Celexa (citalopram hydrobromide) Tablets (NDA 020822)				
20822	S-037	12/24/08	CBE	Approved January 30, 2009
20822	S-038	05/15/09, and amended on 4/1/10, and 11/24/10 (RS to 9/24/10 Agency CR letter), and amended on 6/28/11	PA	Pending
20822	S-040	3/31/10, 7/13/10, 6/28/11 (RS to 12/29/10 Agency CR letter), 6/29/11, and 7/14/11	PA	Pending
Celexa (citalopram hydrobromide) Oral Solution (NDA 021046)				
21046	S-015	12/24/08	CBE	Approved January 30, 2009
21046	S-016	05/15/09, and amended on 4/1/10, and 11/24/10 (RS to 9/24/10 Agency CR letter), and amended on 6/28/11	PA	Pending
21046	S-017	3/31/10, 7/13/10, 6/28/11 (RS to	PA	Pending

		12/29/10 Agency CR letter), 6/29/11, and 7/14/11		
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NOTES

- The last approved labeling, for comparison proposes, was the labeling attached to the January 30, 2009 approval letter for supplement 20822/S-037 & 21046/S-015.
- On May 18, 2009, Forest submitted Prior Approval labeling supplements that contained Comprehensive Medication Guides per our Prior Approval Supplement (PAS) request letter dated April 16, 2009. This request required that across all current generation drugs indicated to treat major depressive disorder (MDD) will be required to have a comprehensive Medication Guide as part of the approved drug label. In effort to standardize the medication guide across the drug class, we asked that the sponsor resubmit the medication guide using the Division of Psychiatry Products template. On March 15, 2010, we sent the sponsor an updated Med Guide template (as there was much variability of the medication guide submission across the drug class) and requested the sponsor to amend their April 16, 2009 PAS. The sponsor submitted their amended comprehensive med guide on April 1, 2010. A complete response letter was issued on September 24, 2010 in response to the sponsor's April 1, 2010 submission.
- On March 31, 2010, Forest submitted Prior Approval labeling supplements that resulted from our findings regarding their Qt studies. As such, QTc information has been added to Contraindications, Warnings, Precautions, Drug Interaction, Adverse Reactions, and Dosage and Administration sections of the label. On June 29, 2011, the sponsor agreed to our label proposal. (b) (4)

REVIEW

20822/S-038

21046/S-016

Date: 5/15/09, and amended on 4/1/10, 11/24/10, and 6/28/11

CBE: No

Reviewed by Medical Officer: Yes

These supplements provide for changes to the Medication Guides to convert it from a standard suicidality Medication Guide to a comprehensive Medication Guide which is product specific per our requests on April 16, 2009, and September 24, 2010.

The changes to the Medication Guide are far too extensive to annotate in an RPM review. The major changes to the Medication Guide include:

- Expanding the current medication guide which describes only the suicidality risks to a comprehensive medication guide that provides information about all important risks, what is Celexa, who should not take Celexa, what the patient should tell his/her provider before taking Celexa, how to take Celexa, what to avoid while taking Celexa, common side effects of Celexa, how to store Celexa, general information about Celexa, and ingredients in Celexa.
- Reducing redundancy and enhancing patient friendly language.

We added one statement to the prescriber's insert to maintain consistency with the Medication Guide. The following statement was added to the Pediatric Use section.

Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as Lexapro.

The Agency and sponsor reached agreement regarding these supplements via email on August 10, 2011.

REVIEW

20822/S-040

21046/S-017

Date: 3/31/10, 7/13/10, 6/28/11, 6/29/11, and 7/14/11

CBE: No

Reviewed by Medical Officer: Yes

- These Prior Approval labeling supplemental new drug applications propose changes to QTc information in the following section of the label (deletions in red and additions in blue)

QT Labeling Changes:

Population Subgroups

20 mg/day is the maximum recommended dose for those who are CYP2C19 poor metabolizers or who are also taking a CYP2C19 inhibitor such as cimetidine, due to the risk of QT prolongation.

Drug-Drug Interactions

Celexa 20 mg/day is the maximum recommended dose for patients taking concomitant cimetidine or another CYP2C19 inhibitor because of the risk of QT prolongation.

CONTRAINDICATIONS

Celexa is contraindicated in patients with congenital long QT syndrome (see WARNINGS, PRECAUTIONS, and Drug Interactions).

WARNINGS

QT-Prolongation and Torsade de Pointes

Citalopram causes dose dependent QT prolongation and should not be dosed above 40 mg/day . Torsade de Pointes has been reported postmarketing. Celexa should not be used in patients with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalations over 20 mg/day in CYP2C19 poor metabolizers or patients taking concomitant cimetidine or another CYP2C19 inhibitor are not recommended.

Individually corrected QTc (QTcNi) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 119 healthy subjects. The maximum mean (upper bound of the 95% one-sided confidence interval) difference from placebo were 8.5 (10.8) and 18.5 (21.0) msec for 20 mg and 60 mg citalopram, respectively. Based on the established exposure-response relationship, the predicted QTcNi change from placebo (upper bound of the 95% one-sided confidence interval) under the C_{max} for the dose of 40 mg is 12.6 (14.3) msec. In those patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, higher citalopram exposure would be expected, along with any concomitant risks.

PRECAUTIONS

Use in Patients with Concomitant Illness

Clinical experience with Celexa in patients with certain concomitant systemic illnesses is limited. Due to the risk of QT prolongation, ECG monitoring is advised when using Celexa in patients with congestive heart failure, bradyarrhythmias, or who are taking medications that prolong the QT interval. Caution is advised in treating patients with diseases or conditions that cause hypokalemia or hypomagnesemia.

QT-Prolongation and Torsade de Pointes

Citalopram causes dose dependent QT prolongation and should not be dosed above 40 mg/day. Torsade de Pointes has been reported postmarketing. Celexa should not be used in patients with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalations over 20 mg/day in CYP2C19 poor metabolizers or patients taking concomitant cimetidine or another CYP2C19 inhibitor are not recommended.

Drug Interactions

Drugs that Prolong the QT interval: ECG monitoring is recommended with concomitant medications that have demonstrated prolongation of the QT interval (see WARNINGS-QT-Prolongation and Torsade de Pointes).

Cimetidine - In subjects who had received 21 days of 40 mg/day Celexa, 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. (b) (4)

Celexa 20 mg/day is the maximum recommended dose for patients taking concomitant cimetidine because of the risk of QT prolongation (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

ECG Changes

~~Electrocardiograms from Celexa (N=802) and placebo (N=241) 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. The only statistically significant drug placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals.~~

In a thorough QT study, Celexa was found to be associated with a dose-dependent increase in the QTc interval (see WARNINGS-QT-Prolongation and Torsade de Pointes).

Electrocardiograms from Celexa (N=802) and placebo (N=241) groups were compared with respect to outliers defined as subjects with QTc changes over 60 msec from baseline

or absolute values over 500 msec post-dose, and subjects with heart rate increases to over 100 bpm or decreases to less than 50 bpm with a 25% change from baseline (tachycardic or bradycardic outliers, respectively). In the Celexa group 1.9% of the patients had a change from baseline in QTcF >60 msec compared to 1.2% of the patients in the placebo group. None of the patients in the placebo group had a post-dose QTcF >500 msec compared to 0.5% of the patients in the Celexa group. The incidence of tachycardic outliers was 0.5% in the Celexa group and 0.4% in the placebo group. The incidence of bradycardic outliers was 0.9% in the Celexa group and 0.4% in the placebo group.

DOSAGE AND ADMINISTRATION

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

Initial Treatment

~~Celexa (citalopram HBr) should be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of no less than one week. Although certain patients may require a dose of 60 mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.~~

Celexa (citalopram HBr) should be administered at an initial dose of 20 mg once daily, with an increase to a maximum dose of 40 mg/day. Dose increase should usually occur in an increment of 20 mg at intervals of no less than one week. Doses above 40 mg/day are not recommended due to the risk of QT prolongation. Additionally, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose.

Special Populations

20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients. 20 mg/day is the maximum recommended dose for CYP 2C19 poor metabolizers or those patients taking cimetidine or another CYP2C19 inhibitor.

The Agency and sponsor reached agreement regarding these supplements via email on August 10, 2011.

CONCLUSIONS

1. The above labeling supplements only provide for the revisions as stated above for these open supplements when compared to the last approved labeling (approval letter dated 1-30-09).
2. sNDA 20822 S-038, sNDA 21046 S-016: The Agency and sponsor reached agreement regarding the addition of QTc information in the label and the new comprehensive medication guide via email on August 10, 2011.
3. sNDA 20822 S-040, sNDA 21046 S-017: The Agency and sponsor reached agreement regarding the addition of QTc information in the label and the new comprehensive medication guide via email on August 10, 2011.
4. The clinical reviewer concurs with the sponsor's proposed changes.
5. I recommend that an approval letter issue for these pending applications.

{See appended electronic signature page}

CDR William H. Bender, R.Ph., MS HCA,
Senior Regulatory Project Manager

{See appended electronic signature page}

Paul David, R.Ph.
Chief, Project Management Staff

Enclosure: Annotated labeling changes

39 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

WILLIAM H BENDER

08/11/2011

PAUL A DAVID

08/11/2011

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND or NDA	20822 /21046 / 21323 / 21365
Brand Name	Celexa
Generic Name	Citalopram Hydrobromide
Sponsor	Forest Research Institute, Inc.
Indication	Depression and Anxiety
Dosage Form	Oral, Immediate-Release Tablets
Drug Class	SSRI
Therapeutic Dosing Regimen	20 mg/day
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	60 mg/day
Submission Number and Date	SDN 139/10 Nov 2008
Clinical Division	DPP / HFD 130

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

A significant QTc prolongation effect of citalopram hydrobromide (20 mg/day and 60 mg/day) was detected in the thorough QT study. Using individually corrected QT (QTcNi) interval, the largest upper bounds of the 2-sided 90% confidence intervals (CI) for the mean difference between citalopram hydrobromide 20 mg and placebo, and between citalopram hydrobromide 60 mg and placebo were 10.8 ms and 21.0 ms at 4 hours post-dose, respectively. Based on the established concentration-QT relationship, the predicted upper bound of 90% CI after the 40-mg dose was 14.3 ms (Table 1). The largest lower bound of the two-sided 90% CI for the baseline-adjusted, placebo-corrected QTcNi ($\Delta\Delta\text{QTcNi}$) for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, multi-center, double-blind, placebo-controlled, crossover study, 119 subjects received citalopram 20 mg/day (Day 9), citalopram 60 mg/day (Day 22), moxifloxacin 400 mg, and placebo. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest UpperBound of $\Delta\Delta QTcNi$ for Citalopram (20 mg/d and 60 mg/d) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcNi$ (ms)	90% CI (ms)
Citalopram 20 mg/d (on Day 9)	4	8.5	(6.2, 10.8)
Moxifloxacin 400 mg (on Day 9)	4	12.2	(9.9, 14.5)*
Citalopram 60 mg/d (on Day 22)	4	18.5	(16.0, 21.0)
Moxifloxacin 400 mg (on Day 22)	4	13.4	(10.9, 15.9)*
Citalopram 40 mg /d [#]	-	12.6	(10.9,14.3) [#]

*Multiple endpoint adjustment was not applied. The largest lower bounds after Bonferroni adjustment for 4 time points for moxifloxacin on Days 9 and 22 are 9.1 ms and 10.0 ms, respectively.

[#] Model predictions based on the concentration-QTc relationship

The highest dose tested in the trial (i.e., 60 mg/day) represents the highest potential therapeutic dose following the current label. CYP3A4 and CYP2C19 are the primary isozymes involved in the metabolism of citalopram. It is anticipated that the exposure increases in a CYP2C19 poor metabolizer and a patient with concomitant cimetidine (inhibitor of multiple CYP450 enzymes) by 1.6 and 1.4 fold, respectively. Therefore, the exposure for a patient taking 60-mg /day dose for the above two scenarios was not covered in the trial.

Considering a 40-mg daily dose which is most commonly used in clinical practice, exposure following 60 mg/day is adequate to cover exposure expected after 40 mg /day in a CYP2C19 poor metabolizer or a patient with concomitant cimetidine. However, the exact fold increase in C_{max} in a patient taking 40-mg dose who is a CYP2C19 poor metabolizer and also takes concomitant cimetidine is unclear but would be likely greater than 1.6-fold (Please refer to QT-IRT protocol review). Exposure increases following a 20-mg dose in elderly patients and hepatically impaired patients is anticipated to be less than the maximum exposure in healthy subjects with a 40-mg dose.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- Given that the C_{max} in a patient taking a 40- or 60-mg dose who is a CYP2C19 poor metabolizer (PM) and also takes concomitant cimetidine would be at least 1.6-fold, mean QTc changes over 20 ms can be expected in such a scenario.
- Based the current package insert (PI), the 60-mg dose has not established additional benefit over 40 mg but is used in some patients. Given the dose dependent QT prolongation observed in this study with a mean effect (90% upper bound) of 18.5 ms (21 ms) we recommend that the division re-evaluates efficacy vs. risk at this dose.

- Based on the current PI, only the 20-mg dose is recommended in the elderly and subjects with hepatic impairment and we concur.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

Sponsor proposes the following text in the label:

Electrocardiograms from Celexa (N=802) and placebo (N=241) 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. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals.

Reviewer's Comment: We recommend deletion of the statement "There were no observed differences in QT or other ECG intervals". The sponsor should only report outlier data i.e. QTcF over 500 ms from the clinical trials.



2.2 QT-IRT'S LABELING RECOMMENDATION

QT_IRT recommendations for labeling are suggestions only; we defer final decisions related to labeling to the review division.

Warning and Precautions

QT-prolongation and Torsade de Pointes

Citalopram causes dose dependent QT prolongation. Torsade de Pointes has been reported post-marketing. Avoid in patients with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalation from 40 mg to 60 mg should be initiated with ECG monitoring in all patients and considered only in the absence of therapeutic alternatives. Dose escalations over 20 mg in CYP 2C19 PM or patients taking concomitant cimetidine is not recommended.

Study description

Individually corrected QTc (QTcNi) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 119 healthy subjects. The maximum mean (95% upper confidence bound) difference from placebo arm were 8.5 (10.8) and 18.5 (21.0) ms for 20-mg and supratherapeutic 60-mg citalopram, respectively. Based on the established exposure-response relationship, the predicted QTcNi change from placebo arm (95% upper confidence interval) under the C_{max} for the dose of 40 mg is 12.6 (14.3) ms. Citalopram 60-mg dose only represents the therapeutic exposure in patients who are not CYP2C19 poor metabolizer or take concomitant cimetidine. Considering a 40-mg dose which is most commonly used in clinical practice, exposure following 60 mg/day is adequate to cover exposure expected after 40 mg /day in a CYP2C19 poor metabolizer or a patient with concomitant cimetidine.

3 BACKGROUND

The Division of Psychiatry Products (DPP) has been conducting an ongoing review of QT prolongation with use of the selective serotonin re-uptake inhibitors (SSRI's), citalopram and escitalopram. The data they have indicate that there is a risk of QT prolongation with these drugs, although the data have limitations and the magnitude of the effect is not clear. The division felt a Thorough QT Study is necessary to assess this risk more definitely, and have asked the sponsor to perform the same in a meeting dated June 10, 2008 (FDA Internal Pre-Meeting June 3, 2008).

The QT-IRT has recently reviewed the TQT study report (see QT-IRT review dated April 27, 2010 for escitalopram under NDA 21323). In this study, the largest upper bounds of the 2-sided 90% confidence interval (CI) for the mean placebo-adjusted, baseline corrected QTcF ($\Delta\Delta QTcF$) difference between escitalopram 10 mg/day, escitalopram 30 mg/day and placebo were 6.4 ms at 4 hours and 12.7 ms at 3 hours after dose, respectively with a positive exposure response relationship.

(Please refer to Clinical review by Dr. Lisa Jones (NDA 21323, NDA 21365, Submission number N000 MP) for details regarding previous clinical experience).

3.1 CLINICAL PHARMACOLOGY

Sponsor did not provide the clinical pharmacology table for Celexa. Section 6.2 summarizes the key features of escitalopram's clinical pharmacology including the information about expected high clinical exposure scenario for citalopram. Please refer to approved label for Celexa (citalopram hydrobromide) for more details.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocols (conducted under NDA 20822/ 21046 / 21323 / 21365) prior to conducting this study. The sponsor submitted the study report CIT-PK-15 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Evaluation of the Effects of Sequential Multiple-Dose Regimens of Citalopram on Cardiac Repolarization in Healthy Subjects

4.2.2 Protocol Number

CIT-PK-15

4.2.3 Study Dates

First Subject Enrollment: April 9th, 2009

Last Subject Enrollment: September 24th, 2009

4.2.4 Objectives

To assess the effects of a therapeutic dose (20 mg/d) and a supra-therapeutic dose (60 mg/d) of citalopram on cardiac repolarization as determined by manual measurement of the heart-rate–corrected QT interval on repeated digitally recorded 12-lead electrocardiograms (ECGs).

4.2.5 Study Description

4.2.5.1 Design

Multi-center, randomized (stratified by sex), double-blind, placebo-controlled, crossover, escalating multiple-dose study. Subjects were randomized into one of six treatment sequences. All doses consisted of two identical-appearing capsules.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was double-blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

All subjects will receive the following treatments:

- Citalopram: Escalating doses of 20-, 40-, and 60-mg /d citalopram. 9 days of citalopram 20 mg/d + 4 days of citalopram 40 mg/d + 9 days of citalopram 60 mg/d.
- Moxifloxacin: 8 days of placebo + a single 400-mg moxifloxacin dose (Day 9) + 12 days of placebo + a single 400-mg moxifloxacin dose (Day 22).
- Placebo: a full course (22 days) of placebo.

Day 9 and/or 22 for each dose group and placebo was calculated relative to the first day of dosing in each treatment period. The three occasions were separated by at least 14 days each.

4.2.6.2 Sponsor's Justification for Doses

“In this study, the effects of a therapeutic dose of 20 mg/d and a supra-therapeutic dose of 60 mg/d citalopram on QT prolongation were tested. According to the ICH E14 guidance, unless precluded by considerations of safety or tolerability owing to adverse effects, the QT interval prolongation of the study drug should be assessed at substantial multiples of the anticipated maximum therapeutic exposure. A supra-therapeutic dose of 60 mg was chosen based on plasma levels obtained from special population, drug-drug interaction and genetic polymorphism studies. Studies in hepatically impaired and elderly subjects (recommended dosage for both groups is 20 mg/d), showed only modest increases in C_{max} (up to 13%) and AUC (50-60%) compared to healthy subjects. Also, since citalopram (CT) is metabolized by multiple enzyme systems, inhibitors of individual CYP isozymes would not be expected to appreciably affect plasma levels of CT. In fact, cimetidine, an inhibitor of multiple CYP450 isozymes, increased C_{max} values of CT by 40%. Finally, a genetic polymorphism study showed that the C_{max} and AUC values in poor metabolizers of mephenytoin (CYP2C19) increased by 60% and 66%, respectively, compared with extensive metabolizers. Collectively, these data suggest that the use of 60 mg/d as the supra-therapeutic dose in this study was justified.”

(Source: Study report CIT-PK-15, Section 9.4.4, Page 36)

Reviewer's Comments.

The highest dose tested in the trial (i.e., 60 mg/day) represents the highest potential therapeutic dose following the current label. CYP3A4 and CYP2C19 are the primary isozymes involved in the metabolism of citalopram. It is anticipated that the exposure increases in a CYP2C19 poor metabolizer and a patient with concomitant cimetidine (inhibitor of multiple CYP450 enzymes) by 1.6- and 1.4-fold, respectively. Therefore, the exposure for a patient taking a 60-mg/day dose for the above two scenarios was not covered in the trial.

Considering a 40-mg dose which is most commonly used in clinical practice, exposure following 60 mg/day is adequate to cover exposure expected after 40 mg /day in a CYP2C19 poor metabolizer or a patient with concomitant cimetidine.

However, the exact increase in C_{max} in a patient taking a 40-mg dose who is a CYP2C19 poor metabolizer and also takes concomitant cimetidine is unclear but would be likely greater than 1.6-fold (Please refer to QT-IRT protocol review). Exposure increases following a 20-mg dose in elderly patients and hepatically impaired patients is anticipated to be less than the maximum exposure in healthy subjects with a 40-mg dose.

4.2.6.3 Instructions with Regard to Meals

“Subjects were dosed with 240 mL of water in the clinic approximately 1 hour after a standard low-fat breakfast on Days -1, Days 1, 8-10, 14-15, 21-22, 37, 44-46, 50 51, 57-58, 73, 80-82, 86-87, and 93-94.

For home dosing, subjects were instructed to take the study drug with 240 mL of water. Subjects were also reminded to take the study drug at the same time each day and to record the dosing time in their diaries. Doses administered at home occurred on Days 2- 7, 11-13, 16-20, 38-43, 47-49, 52-56, 74-79, 83-85, and 88-92.”

Reviewer’s Comments: Acceptable. According to the approved label for Celexa, citalopram can be administered with or without food and absorption is not affected by food.

4.2.6.4 ECG and PK Assessments

Table 2: ECG and PK Sampling Schedule

Study Day	-1	9	22
Intervention	No treatment (Baseline)	Multiple Dose 20 mg (Day 1 to 9)	Multiple dose 60 mg (Day 14 to 22)
12-Lead ECGs	0,1,2,3,4,5,6,7,8,10, 12,14,23 h post dose	Predose, 2,3,4,5,7,12 and 23 h post dose	Predose, 2,3,4,5,7,12 and 23 h post dose
PK Samples for drug	None collected	Predose, 2,3,4,5,7,12 and 24 post dose	Predose, 2,3,4,5,7,12 and 24 post dose

Reviewer’s Comments: The time points for PK and ECG collection are acceptable. Since it was cross over escalating dose design, day 9 and 22 represents PK at a 20-mg and 60-mg daily dose, respectively. Since time-matched PK at 23 h was not available, concentration at 24 h was used instead to match with ECG at 23 h. Based on the concentration-time profile of citalopram, this time shift in PK sampling is acceptable. Moreover, reviewer conducted sensitivity analysis for concentration-QT by removing 23 h time point from the dataset. The results were similar to those obtained using the complete data which are reported in section 5.3.

4.2.6.5 Baseline

The sponsor used time-matched QTc values collected on Day -1 as baseline.

4.2.7 ECG Collection

A central ECG laboratory was employed to minimize variability. To further control variability in interpretation, the central ECG laboratory employed a limited number of skilled readers who were blinded to all study information (e.g., study design, study drug assignment, treatment time, day, time of assessment, subject number, sex, age, and race). The same blinded ECG reader interpreted and reviewed all study-related ECGs for one subject. Blinding was maintained by presenting each ECG reader with a random sequence of ECGs. An assessment of inter-reader variability was performed by having a subset of the tracings (approximately 2%) interpreted by a second reader. Lead II was used as the primary lead for interval measurements and Lead V5 was used as the secondary lead for interval measurements. The baseline and on-treatment ECG were based on the same lead whenever possible.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 119 subjects (67 males, 52 females) between the ages of 19 and 45 years, with a normal baseline ECG and BMI between 20-31 kg/m² were enrolled in the study, and 93 subjects completed it. A total of 26 subjects prematurely discontinued from the study for the following reasons: 4 subjects for AEs, 12 subjects for protocol violation, 7 subjects withdrew consent and 3 subjects were lost to follow-up.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the largest time-matched change from baseline mean differences between citalopram (doses 20 mg/d - 60 mg/d) and placebo in individually corrected QT interval (QTcNi).

Where QTcNi was calculated the following two steps:

First, for each subject, all pre-dose QT/RR data on Days -1, 36, and 72 were fitted to the linear regression model $QT = a_i + b_i \cdot RR + \text{error}$, where a_i is the intercept and b_i is the slope.

Second, the estimated subject-specific slope b_i served as the individual correction parameter for this subject and the individual correction was computed as:

$$QTcNi = QT + b_i (1 - RR)$$

The sponsor used a linear regression model. This model included treatment, period, sex, time, and treatment-by-time interaction as the fixed effects; subject, subject--treatment, and subject-by-time as random effects; time-matched baseline value and baseline-by-time interaction as fixed covariates effect; and an unstructured covariance matrix for within-subject observations.

Table 3 presented the maximum time point means differences of $\Delta\Delta\text{QTcNi}$ for citalopram 20 mg/d, and citalopram 60 mg/d. The largest upper bounds of the 2-sided 90% CIs for the mean differences between citalopram 20 mg/d and placebo, and between citalopram 60 mg/d and placebo were 9.37 ms and 19.47 ms (see Figure 1), respectively. For moxifloxacin 400 mg, the largest lower bounds of the 2-sided 90% CI for the mean differences ranged from 5.02 ms to 10.18 ms (see Table 4).

The sponsor concluded that citalopram 20 mg/d did not result in a clinically significant QTc prolongation. The largest upper bound of 2-sided 90% CI of citalopram 20 mg/d was less than 10 ms. However, the largest upper bound of 2-sided of citalopram 60 mg/d was higher than 10 ms threshold. For moxifloxacin 400 mg, the lower bounds of 2-sided 90% CI were above the 5 ms threshold which demonstrated assay sensitivity.

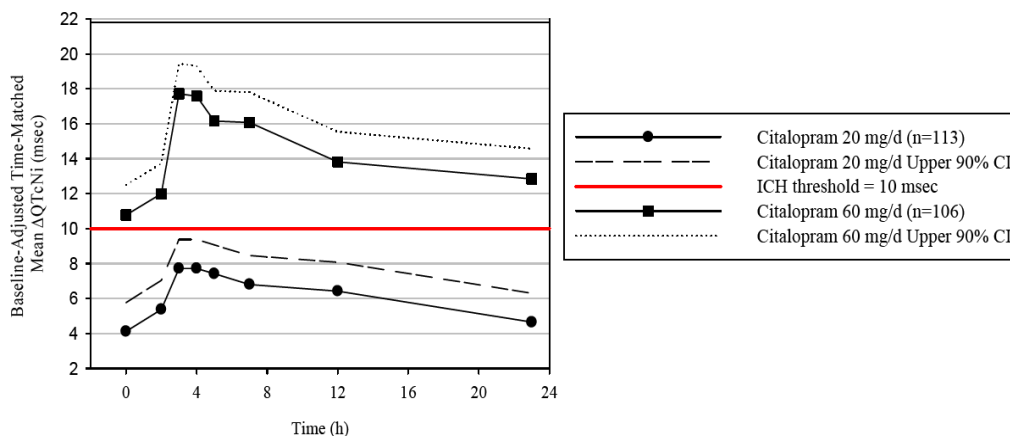
Table 3: Sponsor's Analysis Results of Largest of ΔQTcNi and $\Delta\Delta\text{QTcNi}$ for Citalopram

Treatment	Time-Matched Mean ΔQTcNi		Largest Difference in LSMEAN $\Delta\Delta\text{QTcNi}$	Two-Sided 90% CI For Difference in LSMEAN
	Placebo	Citalopram		
Citalopram 20 mg/d (N=113)	2.64	10.36	7.72	(6.08, 9.37)
Citalopram 60 mg/d (N=106)	-2.77	14.94	17.71	(16.00, 19.42)

Citalopram 20 mg/d= 9 days of citalopram 20 mg/d

Citalopram 60 mg/d= 9 days of citalopram 20 mg/d + 4 days of citalopram 40 mg/d + 9 days of citalopram 60 mg/d.

Figure 1: Sponsor's Time Course of Means and Upper 90% CI $\Delta\Delta\text{QTcI}$ for Citalopram 20 mg/d and Citalopram 60 mg/d



Citalopram 20 mg/d= 9 days of citalopram 20 mg/d

Citalopram 60 mg/d= 9 days of citalopram 20 mg/d + 4 days of citalopram 40 mg/d + 9 days of citalopram 60 mg/d.

Table 4: Sponsor's Analysis Results of $\Delta\Delta\text{QTcNi}$ for Moxifloxacin 400 mg

Timepoint	Average of Moxifloxacin at Day 9 and Day 22 of the Corresponding Treatment Period	
	Time-Matched $\Delta\Delta\text{QTcNi}$	Two-Sided 90% CI For Difference in LSMEAN
0	NA	NA NA
2	8.75	(7.56, 9.94)
3	11.29	(10.12, 12.47)
4	11.37	(10.18, 12.55)
5	9.25	(8.06, 10.43)
7	8.83	(7.65, 10.01)
12	7.69	(6.50, 8.88)
23	6.21	(5.02, 7.41)

NA= Not applicable

Moxifloxacin= 8 days of placebo + a single 400 mg moxifloxacin dose (Day 9) + 12 days of placebo + a single 400 mg moxifloxacin dose (Day 22).

Reviewer's Comments: We will provide our independent analysis results in section 5.2.

4.2.8.2.2 Categorical Analysis

Categorical analysis was used to summarize in the categories of $\text{QTc} > 450$ ms, > 480 ms, and > 500 ms, and changes from baseline $\text{QTc} > 30$ ms and > 60 ms. No subject's absolute $\text{QTc} > 480$ ms and $\Delta\text{QTc} > 60$ ms (see Table 5).

Table 5: Sponsor's Categorical Analysis of ΔQTcNi

Treatment	Day 9			Day 22		
	N	30< to ≤60	>60 msec	N	30< to ≤60 msec	>60 msec
Placebo	105	0 (0.0%)	0 (0.0%)	98	1 (1.0%)	0 (0.0%)
Moxifloxacin	108	12 (11.1%)	0 (0.0%)	101	8 (7.9%)	0 (0.0%)
Citalopram	108	5 (4.6%)	0 (0.0%)	97	29 (29.9%)	0 (0.0%)

Citalopram Day 9= 9 days of citalopram 20 mg/d

Citalopram Day 22= 9 days of citalopram 20 mg/d + 4 days of citalopram 40 mg/d + 9 days of citalopram 60 mg/d.

Moxifloxacin= 8 days of placebo + a single 400 mg moxifloxacin dose (Day 9) + 12 days of placebo + a single 400 mg moxifloxacin dose (Day 22).

4.2.8.3 Safety Analysis

There were no deaths or SAEs in the study. Four subjects discontinued due to non-cardiac adverse events pruritis, contact dermatitis, urticaria and headache with nausea.

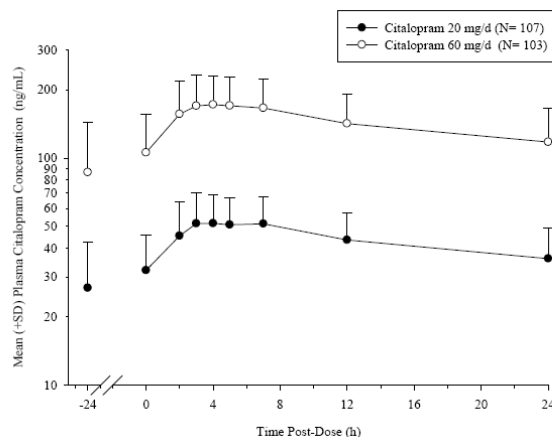
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The pharmacokinetics of citalopram appears to be dose proportional from 20 and 60 mg/kg multiple oral dose. Mean plasma concentration-time profiles of citalopram after 20- and 60-mg multiple oral doses are presented in Figure 2. Summary statistics of the pharmacokinetics of citalopram is provided in Table 6.

The mean C_{max} and $AUC_{(0-t)}$ values after supratherapeutic dose (60 mg) were increased by 3.3- and 3.3-fold, respectively compared to therapeutic dose (20 mg daily).

Figure 2: Mean (+SD) Citalopram Plasma Concentrations (ng/mL) Versus Time — Semi-Log Plot—PK Analysis Population



(Source: Study report CIT-PK-15, Section 11.2.1, Page 66, Fig 11.2.1-1)

Table 6: Pharmacokinetic Parameters (Mean \pm SD) for Citalopram—PK Analysis Population

PK Parameter	Citalopram 20 mg/d, Mean \pm SD (n = 107)	Citalopram 60 mg/d, Mean \pm SD (n = 103)
$C_{max,SS}$, ng/mL	55.99 \pm 17.51	183.59 \pm 59.16
T_{max} , h ^a	4.00 (2.00, 7.07)	4.00 (2.00, 7.02)
$AUC_{0-\tau}$, ng•h/mL	1044.7 \pm 338.2	3433.1 \pm 1215.8
$C_{min,SS}$, ng/mL	36.07 \pm 13.00	117.79 \pm 48.01
C_{av} , ng/mL	43.61 \pm 14.13	143.00 \pm 50.66
Fluctuation, %	47.4 \pm 15.4	48.6 \pm 16.0
Swing, %	59.3 \pm 23.6	61.4 \pm 24.2

^a Median (Min, Max)

Citalopram 20 mg/d= 9 days of citalopram 20 mg/d

Citalopram 60 mg/d= 9 days of citalopram 20 mg/d + 4 days of citalopram 40 mg/d + 9 days of citalopram 60 mg/d.

$C_{max,SS}$ = maximum steady-state plasma drug concentration; T_{max} = time of maximum plasma drug concentration;
 $AUC_{0-\tau}$ = area under the plasma concentration versus time curve during the dosing interval τ at steady-state; $C_{min,SS}$ = minimum steady-state plasma drug concentration; C_{av} = average steady-state plasma drug concentration;
 Fluctuation = peak to trough variation relative to C_{av} ; Swing = peak to trough variation relative to $C_{min,SS}$

(Source: Study report CIT-PK-15, Section 11.2.1, Page 67, Table 11.2.1-1)

4.2.8.4.2 Exposure-Response Analysis

“Construction of the population pharmacokinetic (PopPK) models allowed for a population approach to be taken for estimation of the QTcNi prolongation potential associated with administration of citalopram and moxifloxacin in this study. This nonlinear mixed-effects model approach successfully described the relationship between QTcNi, citalopram (S-CT + R-CT), and moxifloxacin with terms for baseline, placebo, drug effects of moxifloxacin and citalopram, and additive residual error. Due to the high correlation between S-CT and R-CT concentrations, the model could not differentiate the individual contribution of the S- and R-CT enantiomers on QTc prolongation. The QTc prolongation effect of citalopram was adequately characterized by a direct, saturable model of citalopram (S-CT + R-CT) plasma concentrations that was not improved by the addition of the metabolites S-DCT or R-DCT data to the model. The QTc prolongation effect of moxifloxacin was adequately characterized by a direct, linear model of moxifloxacin plasma concentrations.

“Mean QTcNi prolongation at the median C_{max} was estimated for 20- and 60-mg/d citalopram doses to be 8.2 and 15.5 ms, with the upper bound of the two-sided 90% CI at 10.4 and 19.7 ms, respectively.”

For details, please refer to Sponsor’s Pharmacodynamic report, CIT-PK-15 report.

Reviewer’s Comments: Sponsor followed a reasonable approach describing Concentration-QTc relationship. The QTcI used in section 5.5 is same as QTcNi used by the sponsor. We will provide our independent analysis results in section 5.3.

5 REVIEWERS’ ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcNi). Baseline values were excluded in the validation. We used the mixed model of the pooled post-dose data of QTcF and QTcNi distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included gender, baseline, RR, correction type (QTcF or QTcNi), and the interaction term of RR and correction type. The slopes of QTcF and QTcNi versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 7, it appears that QTcNi had smaller absolute slopes than QTcF, which indicates that QTcNi might be a better correction method for the study data.

Table 7: Comparison of QTcF and QTcNi Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcNi	diff_p_value
Citalopram	0.0191	-0.0114	0.0000
Moxifloxacin	0.0214	0.0098	0.0001
Placebo	0.0035	0.0014	0.4211
All	0.0160	0.0024	0.0000

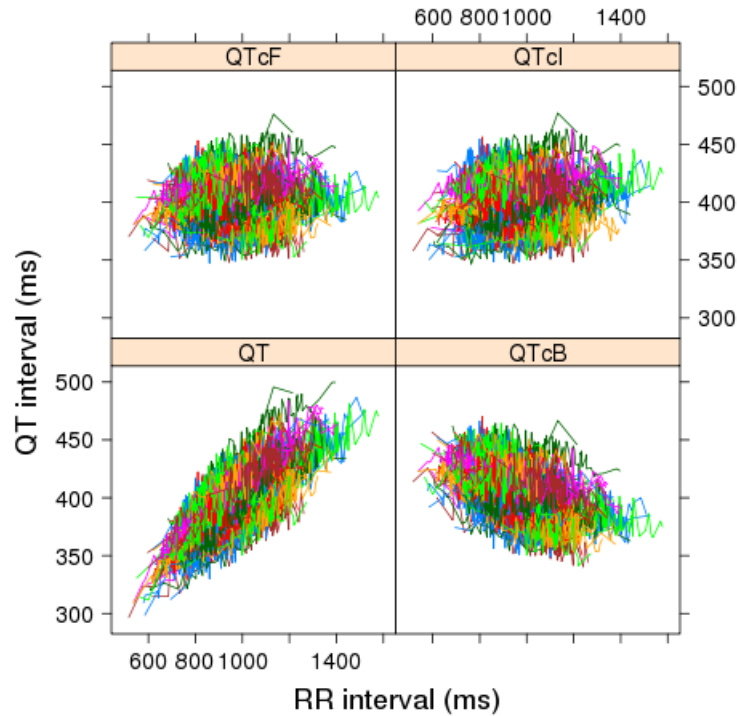
We also confirmed this conclusion by another approach, where we used the mean sum of squared slopes (MSSS) from individual regressions of QTc values versus RR as the criterion. The smaller this value is, the better the correction. Based on the results listed in Table 8, it appears that QTcNi is still the best correction method overall. Therefore, this reviewer used QTcNi for the primary statistical analysis. This is also consistent with the sponsor's choice for the primary endpoint.

Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcNi	
	N	MSSS	N	MSSS	N	MSSS
Citalopram	114	0.0063	114	0.0012	114	0.0013
Moxifloxacin	114	0.0068	114	0.0019	114	0.0016
Placebo	107	0.0066	107	0.0014	107	0.0015
All	119	0.0055	119	0.0008	119	0.0005

The QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI which is same as QTcNi).

Figure 3: QT, QTcB, QTcF, And QTcI (QTcNi) vs. RR (Each Subject's Data Points Are Connected With A Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

The statistical reviewer used mixed model to analyze the Δ QTcNi effect. The model included TIME, PERIOD and SEX as fixed effects and BASELINE as a covariate. The analysis results are presented in Table 9. The largest upper bounds of the two-sided 90% CI for the mean differences between citalopram 20 mg/d (on Day 9) and placebo, and between citalopram 60 mg/d (on Day 22) and placebo are 10.8 ms and 21.0 ms, respectively.

Table 9: Analysis Results of ΔQ_{TcNi} and $\Delta\Delta Q_{TcNi}$ for Citalopram (doses 20 mg/d – 60 mg/d) and Moxifloxacin 400 mg on Days 9 and 22

		Treatment Group							
		Citalopram				Moxifloxacin			
		Placebo	ΔQ_{Tc}	$\Delta\Delta Q_{Tc}$		ΔQ_{Tc}	$\Delta\Delta Q_{Tc}$		
Day	Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	Adj. 90% CI
9	0	-3.3	0.7	4.0	(2.1, 5.8)	-3.7	-0.4	(-2.2, 1.4)	(-2.9, 2.1)
9	2	-4.5	-0.6	3.9	(2.1, 5.7)	3.9	8.4	(6.6, 10.2)	(6.0, 10.8)
9	3	-0.8	7.1	7.9	(5.8, 9.9)	10.6	11.4	(9.4, 13.4)	(8.7, 14.1)
9	4	-0.1	8.4	8.5	(6.2, 10.8)	12.1	12.2	(9.9, 14.5)	(9.1, 15.3)
9	5	4.5	11.5	7.0	(5.2, 8.8)	14.6	10.1	(8.3, 11.8)	(7.6, 12.5)
9	7	1.2	8.0	6.8	(4.8, 8.9)	11.0	9.8	(7.8, 11.8)	(7.1, 12.5)
9	12	1.4	7.3	5.9	(3.9, 7.9)	9.7	8.4	(6.4, 10.3)	(5.7, 11.0)
9	23	-1.0	4.2	5.3	(3.0, 7.5)	5.2	6.2	(4.0, 8.4)	(3.2, 9.2)
22	0	-4.6	5.8	10.4	(8.2, 12.5)	-4.9	-0.3	(-2.4, 1.9)	(-3.2, 2.6)
22	2	-4.3	6.4	10.8	(8.5, 13.0)	3.7	8.1	(5.9, 10.2)	(5.1, 11.0)
22	3	-2.4	15.7	18.1	(15.8, 20.4)	9.9	12.3	(10.1, 14.5)	(9.2, 15.3)
22	4	-2.2	16.3	18.5	(16.0, 21.0)	11.2	13.4	(10.9, 15.9)	(10.0, 16.8)
22	5	4.1	20.0	15.9	(14.0, 17.7)	13.8	9.7	(7.9, 11.4)	(7.3, 12.1)
22	7	0.6	16.5	15.9	(13.7, 18.1)	9.7	9.2	(7.1, 11.3)	(6.3, 12.0)
22	12	0.6	13.6	12.9	(10.7, 15.1)	8.2	7.5	(5.3, 9.7)	(4.5, 10.5)
22	23	-2.6	10.4	13.1	(11.0, 15.1)	2.7	5.3	(3.3, 7.3)	(2.5, 8.0)

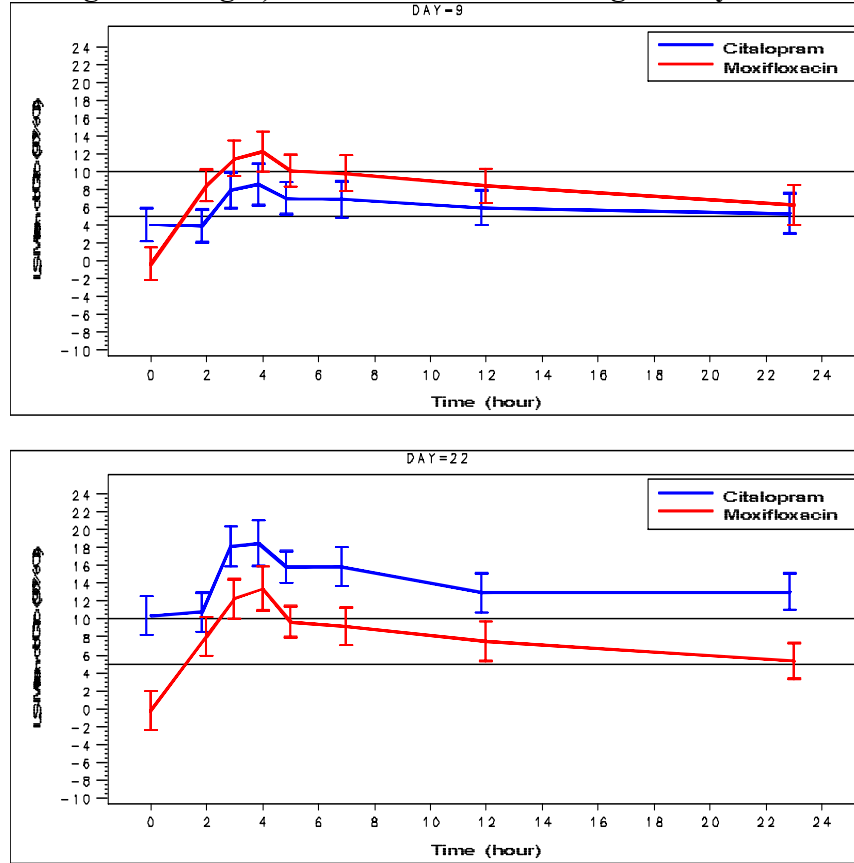
5.2.1.1 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence intervals for moxifloxacin on Days 9 and 22 are 9.9 ms and 10.9 ms, respectively. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence intervals are 9.1 ms and 10.0 ms, respectively.

5.2.1.2 Graph of $\Delta\Delta Q_{TcNi}$ Over Time

The following figure (Figure 4) displays the time profile of $\Delta\Delta Q_{TcNi}$ for different treatment groups on Days 9 and 22.

Figure 4: Time Course of Means and 90% CI $\Delta\Delta\text{QTcNi}$ for Citalopram (Doses 20 mg/d - 60 mg/d) and Moxifloxacin 400 mg on Days 9 and 22



5.2.1.3 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcNi values are ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcNi is above 480 ms.

Table 10: Categorical Analysis for QTcNi

	Total N	Value \leq 450 ms	450 ms<Value \leq 480 ms
Citalopram	109	103 (94.5%)	6 (5.5%)
Moxifloxacin	111	104 (93.7%)	7 (6.3%)
Placebo	106	105 (99.1%)	1 (0.9%)

Table 11 lists the categorical analysis results for ΔQTcNi . No subject's change from baseline is above 60 ms.

Table 11: Categorical Analysis of Δ QTcNi

	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms
Citalopram	108	74 (68.5%)	34 (31.5%)
Moxifloxacin	109	92 (84.4%)	17 (15.6%)
Placebo	105	104 (99.0%)	1 (1.0%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper bounds of the two-sided 90% CI for the mean differences between citalopram 20 mg/d (on Day 9) and placebo, and between citalopram 60 mg/d (on Day 22) and placebo are 3.3 ms and 4.6 ms, respectively. Table 13 presents the categorical analysis of PR, five subjects in citalopram treatment group experienced absolute PR interval greater than 200 ms. Table 14 presents the list of individual subjects with PR \geq 200 ms in treatment groups.

Table 12: Analysis Results of Δ PR and $\Delta\Delta$ PR for Citalopram (20 mg/d -60 mg/d) and Moxifloxacin 400 mg on Days 9 and 22

		Treatment Group						
		Citalopram				Moxifloxacin		
		Placebo	Δ PR	$\Delta\Delta$ PR		Δ PR	$\Delta\Delta$ PR	
Day	Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
9	0	-2.5	-3.3	-0.8	(-3.0, 1.5)	-3.2	-0.7	(-3.0, 1.5)
	2	-3.0	-2.6	0.4	(-1.7, 2.5)	-1.5	1.4	(-0.6, 3.5)
	3	-0.9	-2.2	-1.3	(-3.3, 0.7)	-1.1	-0.2	(-2.1, 1.8)
	4	-1.8	-2.5	-0.7	(-2.7, 1.4)	-0.7	1.2	(-0.9, 3.2)
	5	0.4	0.5	0.1	(-2.0, 2.2)	-0.9	-1.3	(-3.5, 0.8)
	7	0.3	0.1	-0.2	(-2.1, 1.6)	-0.2	-0.5	(-2.3, 1.3)
	12	-0.4	0.9	1.3	(-0.7, 3.3)	1.5	1.9	(-0.0, 3.8)
	23	-0.1	-1.0	-0.8	(-3.0, 1.3)	0.1	0.3	(-1.9, 2.4)
22	0	-2.1	-2.4	-0.3	(-2.8, 2.2)	-2.0	0.1	(-2.3, 2.6)
	2	-2.1	-2.5	-0.4	(-2.9, 2.0)	-0.9	1.2	(-1.2, 3.6)
	3	-1.6	-1.3	0.3	(-2.0, 2.6)	-0.2	1.4	(-0.8, 3.6)
	4	-2.0	-0.9	1.1	(-1.3, 3.4)	-2.3	-0.3	(-2.6, 2.0)
	5	0.3	1.5	1.2	(-1.0, 3.4)	-0.9	-1.1	(-3.2, 1.0)
	7	1.0	1.1	0.1	(-2.1, 2.3)	-0.5	-1.5	(-3.6, 0.6)
	12	-0.9	1.4	2.2	(-0.2, 4.6)	1.3	2.2	(-0.2, 4.6)
	23	-0.8	-0.7	0.2	(-2.1, 2.4)	0.9	1.7	(-0.5, 4.0)

Table 13: Categorical Analysis of PR

	Total N	PR < 200 ms	PR ≥200 ms
Citalopram	109	104 (95.4%)	5 (4.6%)
Moxifloxacin	111	107 (96.4%)	4 (3.6%)
Placebo	106	101 (95.3%)	5 (4.7%)

Table 14: List of Subjects with PR ≥ 200 ms

Subject ID	Treatment	Day	Time (h)	PR at Baseline	PR at Post- Dose	PR Change
CIT-PK-15.0011013	Citalopram	9	2	213.7	214.0	0.3
	Citalopram	22	2	213.7	201.3	-12.3
	Citalopram	9	3	208.0	201.7	-6.3
	Citalopram	22	3	208.0	208.3	0.3
	Citalopram	22	4	212.0	202.7	-9.3
	Citalopram	9	5	218.3	212.7	-5.7
	Citalopram	22	5	218.3	201.0	-17.3
	Citalopram	9	7	215.7	203.7	-12.0
	Citalopram	22	7	215.7	214.7	-1.0
	Citalopram	9	12	217.3	214.3	-3.0
	Citalopram	9	23	208.0	217.0	9.0
	Citalopram	22	23	208.0	212.0	4.0
CIT-PK-15.0011019	Citalopram	9	2	189.7	200.3	10.7
CIT-PK-15.0012018	Citalopram	22	2	190.0	212.3	22.3
	Citalopram	9	3	187.0	211.3	24.3
	Citalopram	22	3	187.0	221.3	34.3
	Citalopram	22	4	186.0	216.0	30.0
	Citalopram	9	5	196.0	228.7	32.7
	Citalopram	22	5	196.0	223.7	27.7
	Citalopram	9	7	187.0	202.3	15.3
	Citalopram	22	7	187.0	217.7	30.7
	Citalopram	9	12	202.3	204.7	2.3
	Citalopram	22	12	202.3	218.3	16.0
	Citalopram	9	23	202.3	212.0	9.7
	Citalopram	22	23	202.3	224.0	21.7
CIT-PK-15.0021069	Citalopram	9	23	.	208.0	.

Subject ID	Treatment	Day	Time (h)	PR at Baseline	PR at Post-Dose	PR Change
CIT-PK-15.0021077	Citalopram	9	2	225.0	200.0	-25.0
	Citalopram	22	2	225.0	206.7	-18.3
	Citalopram	9	3	215.0	212.3	-2.7
	Citalopram	22	3	215.0	204.7	-10.3
	Citalopram	9	4	227.0	216.7	-10.3
	Citalopram	9	5	203.7	234.0	30.3
	Citalopram	22	5	203.7	209.0	5.3
	Citalopram	9	7	214.7	210.0	-4.7
	Citalopram	22	7	214.7	203.3	-11.3
	Citalopram	9	23	206.7	202.0	-4.7
	Citalopram	22	23	206.7	207.0	0.3

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15. The largest upper bounds of the two-sided 90% CI for the mean differences between citalopram 20 mg/d (on Day 9) and placebo, and between citalopram 60 mg/d (on Day 22) and placebo are 0.7 ms and 1.1 ms, respectively. There are no subjects who experienced absolute QRS interval greater than 110 ms in citalopram treatment groups.

Table 15: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Citalopram (20mg/d - 60 mg/d) and Moxifloxacin 400 mg on Days 9 and 22

			Treatment Group					
			Citalopram			Moxifloxacin		
			Placebo	Δ QRS	$\Delta\Delta$ QRS	Δ QRS	$\Delta\Delta$ QRS	
Day	Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
9	0	-0.7	-0.8	-0.1	(-0.9, 0.7)	-0.3	0.3	(-0.4, 1.1)
	2	0.7	-0.2	-0.9	(-1.7, -0.1)	0.4	-0.3	(-1.1, 0.5)
	3	0.4	-0.1	-0.6	(-1.2, 0.1)	0.5	0.0	(-0.6, 0.7)
	4	0.6	0.2	-0.4	(-1.2, 0.3)	0.8	0.2	(-0.5, 0.9)
	5	1.5	0.6	-0.9	(-1.6, -0.2)	1.3	-0.2	(-0.9, 0.5)
	7	1.8	0.9	-0.9	(-1.7, -0.1)	0.6	-1.2	(-1.9, -0.4)
	12	0.8	0.6	-0.2	(-0.9, 0.5)	0.8	0.0	(-0.7, 0.7)
	23	0.2	-0.1	-0.3	(-1.0, 0.4)	-0.0	-0.2	(-0.9, 0.5)

		Treatment Group						
		Citalopram				Moxifloxacin		
		Placebo	Δ QRS	$\Delta\Delta$ QRS		Δ QRS	$\Delta\Delta$ QRS	
Day	Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
22	0	-0.8	-0.5	0.3	(-0.6, 1.1)	-0.6	0.2	(-0.7, 1.1)
	2	0.5	-0.1	-0.6	(-1.4, 0.3)	0.1	-0.4	(-1.2, 0.5)
	3	0.8	0.2	-0.7	(-1.4, 0.1)	0.3	-0.5	(-1.3, 0.3)
	4	0.1	-0.3	-0.4	(-1.2, 0.4)	0.5	0.4	(-0.4, 1.1)
	5	1.4	1.0	-0.4	(-1.3, 0.4)	1.1	-0.3	(-1.1, 0.5)
	7	1.6	1.0	-0.7	(-1.5, 0.2)	0.8	-0.9	(-1.6, -0.1)
	12	0.6	0.1	-0.5	(-1.3, 0.4)	0.2	-0.4	(-1.2, 0.4)
	23	0.3	0.3	-0.0	(-0.8, 0.8)	-0.2	-0.5	(-1.3, 0.3)

Table 16: Categorical Analysis of QRS

	Total N	QRS < 110 ms	QRS \geq 110 ms
Citalopram	109	109 (100%)	0 (0.0%)
Moxifloxacin	111	111 (100%)	0 (0.0%)
Placebo	106	105 (99.1%)	1 (0.9%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The pharmacokinetic characteristics of citalopram were summarized in Table 6 and Figure 2.

The relationship between $\Delta\Delta$ QTcI (QTcNi used by the sponsor) and citalopram concentrations was investigated by linear mixed-effects modeling. Log concentrations were used for the concentration-QT analysis. The following linear models were considered:

- Model 1: Linear model with intercept
- Model 2: Linear model with intercept fixed to zero
- Model 3: Linear model with no intercept

Sponsor had two dose levels with Day 9 representing the 20 mg dose and Day 22 representing the 60 mg dose. Figure 5 (top left) has same symbols for both the dose levels. Complete data from both the dose levels was utilized in the concentration-QT analysis.

Model 1 was chosen since it fitted the data best based on the AIC and BIC criteria. The concentration- $\Delta\Delta$ QTcI relationship for citalopram is visualized in Figure 5 where raw data (20- and 60-mg dose) is shown on the top together with

the population prediction (solid red line). The goodness-of-fit is illustrated in the top right graph of Figure 5 showing the observed median-quantile concentrations and associated mean $\Delta\Delta\text{QTcI}$ (90% CI) together with the mean (90% CI) predicted $\Delta\Delta\text{QTcI}$ (black line with shaded grey area).

The mean (90% CI) predicted $\Delta\Delta\text{QTcI}$ at mean C_{max} of 20 and 60 mg/day are presented in Table 18 and the bottom left and right graph of Figure 5. The results are similar to the sponsor's results summarized in 4.2.8.4.2. $\Delta\Delta\text{QTcI}$ was also predicted for the mean predicted C_{max} (105.2 ng/ml) after 40-mg dose since it is the frequently used dose in clinical practice.

Table 17 summarizes the results for citalopram concentration- $\Delta\Delta\text{QTcI}$ analysis. The slope of the exposure-response relationship is positive ($P < 0.0001$) which implies that $\Delta\Delta\text{QTcI}$ would increase with increasing citalopram concentrations.

Table 17: Exposure-Response Analysis of Citalopram.

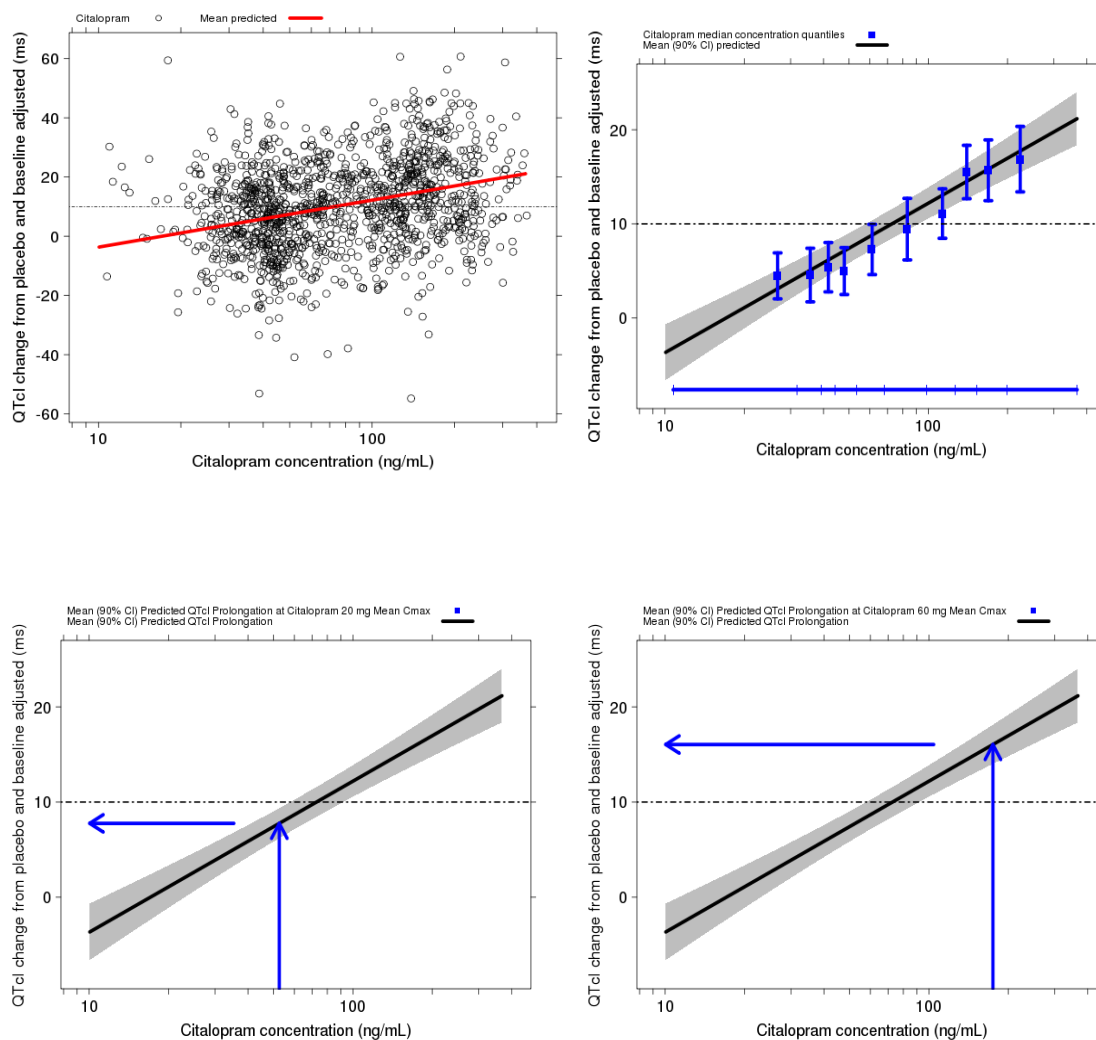
	Estimate (90% CI) p-value	Between Subject Variability (SD)
Model 1: $\Delta\Delta\text{QTcI} = \text{Intercept} + \text{slope} * \text{Citalopram Concentration}$		
Intercept (ms)	-19.6 (-25.4, -13.7) <0.0001	26.6
Slope (ms per log ng/ml)	6.9 (5.5, 8.3) <0.0001	6.05
Residual Variability	11.2	--

Table 18: Predicted Change of $\Delta\Delta\text{QTcI}$ Interval At Mean Peak Citalopram Concentration Using Model 1.

Dose Group	Predicted change in $\Delta\Delta\text{QTcI}$ interval (ms)	
	Mean	90% Confidence Interval
20 mg/day		
Mean C_{max} : 52.6 ng/ml	7.8	6.2, 9.3
40 mg/day		
Mean C_{max} : 105.2 ng/ml*	12.6	10.9, 14.3
60 mg/day		
Mean C_{max} : 175 ng/ml	16	14, 18.1

* Based on linear PK of citalopram, C_{max} at 40 mg is predicted to be double of the C_{max} observed at 20 mg dose

Figure 5: $\Delta\Delta$ QTcI vs. Citalopram Concentration Observed Data 20 and 60 mg/day (Top left), Concentration Quantile Plot (Top right), And Predicted $\Delta\Delta$ QTcI At Mean 20 mg C_{max} (Bottom left) and At Mean 60 mg C_{max} (Bottom Right)



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety Assessments

None of the events identified to be of clinical importance per the ICH E-14 guidelines i.e. sudden cardiac death, syncope, seizure and significant ventricular arrhythmias occurred in this study.

5.4.2 ECG Acquisition and Interpretation

Waveforms in the ECG warehouse were reviewed. According to ECG warehouse statistics, over 94% of the ECGs were read in primary lead (II) with Lead V2 or V5 being the usual alternate leads. According to the automated algorithm, less than 0.2% of the ECGs had significant QT bias. Overall ECG acquisition and interpretation in this study seems acceptable.

5.4.3 PR and QRS Interpretation

There were no clinically relevant effects on the PR and QRS intervals. As indicated in the statistical reviewer's analysis, there were no mean trends and no subject with a post-dose PR of over 200 ms on citalopram had a change from baseline over 25%.

5.4.4 MGPS datamining analysis

An MGPS datamining analysis of AERS was conducted. The lower bound of the 90% confidence interval (EB05) for the signal score (EBGM value) for TdP was greater than 2 (3.4) indicating an incidence greater than twice the expected rate for other drugs. On review of the cases several of them occurred in elderly with co-morbidities and concomitant medications or in the overdose setting, but some of the cases had much clearer associations- see examples below

"This authority report received from (b) (6) affiliate in (b) (6) concerns a 24-year old Iranian female that experienced syncope, torsades de pointes, and ventricular tachycardia during citalopram therapy; cramps and long Q-T syndrome following the discontinuation of drug, and tremor on an unspecified date. It was reported that the patient had been in Norway for approximately ten months, during which time she initiated treatment with citalopram. Citalopram 30-mg daily was started for depression on 11/12/00, followed by "sudden syncope" which occurred on 11/20/00 and 11/27/00. The syncopal episode on 11/27/00 occurred "while attached to an R-test" (a long-term ECG monitoring test) which showed fast ventricular tachycardia (VT) characteristic of Torsade de pointes. On (b) (6), the patient was admitted to a local hospital, the patient experienced several relatively short episodes of VT, and Citalopram was discontinued on 11/28/00. On (b) (6), the patient had VT for 2.5 minutes in conjunction with cramps and syncope. She was electro-converted twice and had a temporary pacemaker placed. On (b) (6), she was transferred to a central hospital, her condition stabilized, and she was discharged on (b) (6) with the diagnosis of long Q-T syndrome (interval value NOS). The patient showed no arrhythmias with readmission to the local hospital (b) (6). The

results of a 24-hour ECG done on 12/18/00 showed sinus rhythm with few ventricular extra systoles. Concomitant medications were reported as not available and relevant medical history included QT prolongation. An ECG done in 4/00 showed a QT (corrected) of 540 ms.

Reviewer's Comment: This patient had congenital long-QT syndrome, with TdP triggered by citalopram. Given the long terminal half life of citalopram (over 30 hours for parent and > 50 hours for metabolite), the events 2-3 days after drug discontinuation might have still been related to citalopram.

“This is a spontaneous report from the U.S. A physician reported via a sales representative that a 23-year-old female patient experienced QT interval changes and cardiac arrest while on Celexa (citalopram) therapy. Following 5 days of therapy with Celexa 20 mg daily (indication and therapy dates unknown), the patient experienced QT interval changes and cardiac arrest. The physician reported that this 23-year-old female with history of four previous syncopal episodes experienced "probable ventricular fibrillation (VF) arrest following probable Torsades with prolonged QT syndrome". Medical history is significant for 4 fainting episodes, all of which she recovered from spontaneously and without sequelae; the physician confirmed that no evaluation/work-up was performed. On 2/27/02, Celexa 20 mg daily was commenced for depression. On (b) (6), the patient lost consciousness as witnessed by her parents. The patient suddenly became unresponsive, turned quite pale, and stiffened. The father could not palpate a pulse and commenced CPR. The patient became very rigid and began frothing at the mouth. When the paramedics arrived, the patient was seizing. The first rhythm obtained was sinus tachycardia. Upon arrival to the emergency room, the patient regained consciousness spontaneously.

“On (b) (6), the patient was implanted with an implantable cardioverter-defibrillator (ICD). The patient tolerated the procedure well and was discharged the following day with Darvocet (propoxyphene) as the only discharge medication. A post-procedure ECG showed sinus rhythm at 53 bpm with an IMI pattern consisting of inverted T-waves in Leads II, III and aVF and somewhat flattened T-waves in V3 through V6, and "with what appeared to be" U-waves as well in these same leads. The physician thought this ECG was likely comparable to the one recorded shortly after her arrest. The reporting physician assessed causality as related to Celexa since the extensive work-up by cardiology (including EP study), neurology, and infectious disease were all negative, and no other etiology was determined. Since the ICD placement, the patient has done well. The physician denied any concomitant medications to Celexa therapy.”

Reviewer's Comment: There is clear association to study drug in this case.

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic (S) **Run ID:** 3805

Dimension: 2 **Selection Criteria:** Generic name(Citalopram) + PT(...) **Where:** EBGM > 2.0

6 rows Sorted by Generic name, EBGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Citalopram	Electrocardiogram QT prolonged	ECG investigations	206	5.59	4.98	6.26
Citalopram	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	63	4.20	3.40	5.14
Citalopram	Electromechanical dissociation	Ventricular arrhythmias and cardiac arrest	14	3.17	2.02	4.79
Citalopram	Rhythm idioventricular	Ventricular arrhythmias and cardiac arrest	3	2.78	1.04	6.60
Citalopram	Ventricular tachycardia	Ventricular arrhythmias and cardiac arrest	67	2.11	1.72	2.57
Citalopram	Cardio-respiratory arrest	Ventricular arrhythmias and cardiac arrest	141	2.09	1.82	2.40

ID:	3805
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As of date:	09/15/2010 00:00:00
Item variables:	Generic name, PT
Stratification variables:	Standard strata
Highest dimension:	2
Minimum count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base counts on cases:	Yes
Use "all drugs" comparator:	No
Apply Yates correction:	Yes
Stratify PRR and ROR:	No
Fill in hierarchy values:	Yes
Exclude single itemtypes:	Yes
Fit separate distributions:	Yes
Save intermediate files:	No
Created by:	(b) (4)
Created on:	09/25/2010 15:40:37 EDT
User:	(b) (4)

Source database:

Source Data: CBAERS data from Extract provided by CBER as of 09/15/2010 00:00:00
loaded on 2010-09-24 14:44:47.0

Dimension: 2 Selection Criteria: Generic name(Citalopram) + PT(Accelerated idioventricular rhythm, Cardiac arrest, Cardiac arrest neonatal, Cardiac death, Cardiac fibrillation, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Convulsion, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Electromechanical dissociation, Parasystole, Presyncope, Rhythm idioventricular, Sudden cardiac death, Sudden death, Syncope, Torsade de pointes, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia) **Where:** EBGM > 2.0

```
SELECT * FROM OutputData_3805 WHERE (DIM=2 AND EBGM>2.0 AND ((P1='D' AND ITEM1 IN ('Citalopram') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Cardiac arrest','Cardiac arrest neonatal','Cardiac death','Cardiac fibrillation','Cardio-respiratory arrest','Cardio-respiratory arrest neonatal','Convulsion','Electrocardiogram QT interval','Electrocardiogram QT interval abnormal','Electrocardiogram QT prolonged','Electromechanical dissociation','Parasystole','Presyncope','Rhythm idioventricular','Sudden cardiac death','Sudden death','Syncope','Torsade de pointes','Ventricular arrhythmia','Ventricular asystole','Ventricular extrasystoles','Ventricular fibrillation','Ventricular flutter','Ventricular pre-excitation','Ventricular tachyarrhythmia','Ventricular tachycardia')))) ORDER BY ITEM1,EBGM desc
```

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

6 APPENDIX

6.1 TABLE OF STUDY ASSESSMENTS

SCHEDULE OF EVALUATIONS: Study CIT-PK-15 (1 of 2)																													
	Screening ^a	Period I																	Period II										
STUDY DAY	-22 to -2	-2	-1	1	2-6	7	8	9	10	11-12	13	14	15	16-19	20	21	22	23	24-34	35	36	37	38-42	43	44	45	46	47-48	
Informed consent	X																												
Adverse events ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, chemistry, urinalysis	X																												
MMNI	X																												
Serology	X																												
Drugs-of-abuse screen	X	X																		X									
Pregnancy test	X ^c	X ^d																		X ^d									
Vital signs (blood pressure, pulse) ^e	X						X	X				X	X				X	X								X	X		
Vital signs (respiration rate, weight, height, temperature)	X																												
Pharmacokinetic blood samples ^f							X	X	X							X	X	X								X	X	X	
Holter electrocardiograms ^g				X	X			X	X								X	X			X	X					X	X	
Standard safety electrocardiograms ^h	X			X				X	X									X	X								X	X	
Physical examination	X																												
Prior and concomitant medications	X	X		X		X			X		X	X			X			X		X				X				X	
Medical and surgical history	X																												
Dosing of study drug				X	X ⁱ	X ⁱ	X	X	X		X ⁱ	X ⁱ	X	X ⁱ	X ⁱ	X	X					X	X ⁱ	X ⁱ	X	X	X	X ⁱ	
Admission to clinic ^j		X				X						X				X				X				X					
Meals and/or snacks (site provided) ^k		X	X	X		X	X	X	X		X	X	X		X	X	X	X		X	X	X		X	X	X	X	X	
Discharge from clinic ^l				X					X				X					X				X						X	

a Must be done within 21 days before Day -1.

b Adverse events will be collected for up to 30 days after EOS.

c Serum pregnancy test.

d Serum or urine pregnancy test.

e Vital sign evaluations at Screening and EOS and on Days 9, 14, 22, 45, 50, 58, 81, 86, and 94 at 0.0 hour (predose) and 1, 2, 4, 6, and 24 hours postdose.

f PK blood samples on Days 9, 22, 45, 58, 81, and 94 at 0.0 hour (predose) and 2, 3, 4, 5, 7, 12, and 24 hours postdose and on Days 8, 21, 44, 57, 80, and 93 at 0.0 hour (predose).

g Holter ECGs on Days -1, 36, and 72 at 0800 hours and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 23 hours after 0800 hours and on Days 9, 22, 45, 58, 81, and 94 at 0.0 hour (predose) and 2, 3, 4, 5, 7, 12, and 23 hours postdose.

h Standard safety ECGs at Screening and EOS; on Day 1 at 0.0 hour (predose); and on Days 9, 22, 45, 58, 81, and 94 at 0.0 hour (predose) and 2 and 24 hours postdose.

i Home dosing

j Admission to clinic will be at approximately 1900 hours.

k Meal times: breakfast, 0700 hours; lunch, 1200 hours; dinner, 1800 hours; and snack, 2100 hours.

l Discharge from the clinic on Days 23, 59, and 95 after the PK blood sample; on Days 1, 10, 37, 46, 73, and 82 after dosing; and on Days 15, 51, and 87 at least 4 hours after dosing.

ECG = electrocardiogram, electrocardiographic; EOS = end of study; PK = pharmacokinetic.

SCHEDULE OF EVALUATIONS: Study CIT-PK-15 (2 of 2)																												
	Period II										Period III																	
STUDY DAY	49	50	51	52-53	56	57	58	59	60-70	71	72	73	74-78	79	80	81	82	83-84	85	86	87	88-91	92	93	94	95	End of Study ^a	Poststudy ^b
Informed consent																												
Adverse events ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, chemistry, urinalysis																											X	
Serology																												
Drugs-of-abuse screen										X																		
Pregnancy test										X ^d																	X ^e	
Vital signs (blood pressure, pulse) ^f		X	X				X	X							X	X				X	X				X	X	X	
Vital signs (respiration rate, weight, height, temperature)																											X ^f	
Pharmacokinetic blood samples ^g							X	X	X						X	X	X							X	X	X		
Holter electrocardiograms ^h							X	X			X	X			X	X									X	X		
Standard safety electrocardiograms ⁱ							X	X							X	X									X	X	X	
Physical examination																											X	
Prior and concomitant medications	X		X		X			X		X	X					X		X		X			X			X	X	
Medical and surgical history																												
Dosing of study drug	X ^j	X	X	X ^j	X ^j	X	X				X	X ^j	X ^j	X	X	X	X ^j	X ^j	X	X	X ^j	X ^j	X	X				
Study Drug compliance assessment																											X	
Admission to clinic ^k	X				X					X					X				X				X					
Meals and/or snacks (site provided) ^l	X	X	X		X	X	X	X		X	X	X		X	X	X	X	X	X	X	X		X	X	X	X		
Discharge from clinic ^m			X					X			X					X					X					X		

a Must be done within 7 days of the final PK sample on Day 95 or at ET Visit.

b Must be done 7 days after the EOS or ET Visit.

c Adverse events will be collected for up to 30 days after EOS.

d Serum or urine pregnancy test.

e Vital sign evaluations at Screening, EOS, and on Days 9, 14, 22, 45, 50, 58, 81, 86, and 94 at 0.0 hour (predose) and 1, 2, 4, 6, and 24 hours postdose.

f Measurement of height is not required at EOS.

g PK blood samples on Days 9, 22, 45, 58, 81, and 94 at 0.0 hour (predose) and 2, 3, 4, 5, 7, 12, and 24 hours postdose and on Days 8, 21, 44, 57, 80, and 93 at 0.0 hour (predose).

h Holter ECGs on Days -1, 36, and 72 at 0800 hours and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 hours after 0800 hours and on Days 9, 22, 45, 58, 81, and 94 at 0.0 hour (predose) and 2, 3, 4, 5, 7, 12, and 24 hours postdose.

i Standard safety ECGs at Screening and EOS; on Day 1 at 0.0 hour (predose); and on Days 9, 22, 45, 58, 81, and 94 at 0.0 hour (predose) and 2 and 24 hours postdose.

j Home dosing.

k Admission to clinic will be at approximately 1900 hours.

l Meal times: breakfast, 0700 hours; lunch, 1200 hours; dinner, 1800 hours; and snack, 2100 hours.

m Discharge from the clinic on Days 23, 59, and 95 after the PK blood sample; on Days 1, 10, 37, 46, 73, and 82 after dosing; and on Days 15, 51, and 87 at least 4 hours after dosing.

ECG = electrocardiogram, electrocardiographic; EOS = end of study; ET = early termination; PK = pharmacokinetic.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

HAO ZHU
10/11/2010

NITIN MEHROTRA
10/11/2010

MOH JEE NG
10/12/2010

JOANNE ZHANG
10/12/2010

SUCHITRA M BALAKRISHNAN
10/12/2010

NORMAN L STOCKBRIDGE
10/12/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020822Orig1s038, s040

021046Orig1s016, s017

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Bender, William

From: Bender, William
Sent: Wednesday, August 10, 2011 5:33 PM
To: 'Sengupta, Debleena'
Subject: RE: Celexa Label
Attachments: DearDrCelexa HCP Letter 08_04_2011-tracked (3).doc

Hi Debleena,

I have checked with the team and we concur with your edits to the PI. Therefore, this email is agreement to the labeling supplements.

We do have one edit to your DHCP letter--p1, second paragraph. Please see the track change (though we do not approve DHCP as previously discussed).

Best regards,
Bill

From: Sengupta, Debleena [mailto:Debleena.Sengupta@frx.com]
Sent: Friday, August 05, 2011 9:38 AM
To: Bender, William
Subject: RE: Celexa Label

Dear Bill,

I met with the team and for the most part we agree with the Agency's edits, but still had a few edits on the PI and the Dear HCP letter. Lines 310-313, we felt that it was no longer appropriate to maintain sentences concerning methodology, since we do not want patients to take 60 mg of Celexa.

Please see attached clean and tracked versions of both.

As discussed, we will submit a PLR after the supplements have been approved.

Regards,
Debleena

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Wednesday, July 27, 2011 3:00 PM
To: Sengupta, Debleena
Subject: Celexa Label

Hi Debleena,

As promised, attached is our label in the "traditional" label as the PLR was never approved. Please let me know if you accept these changes. If you do, your email will be our final agreement.

Thanks,
Bill

P.S. After the approval of these supplements, please submit a new PLR supplement for Celexa (as discussed).

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

/s/

WILLIAM H BENDER
08/10/2011

Bender, William

From: Bender, William
Sent: Monday, June 20, 2011 8:57 AM
To: 'Sengupta, Debleena'
Subject: RE: Celexa QT PI label and MedGuide
Follow Up Flag: Follow up
Flag Status: Red

Good Morning Debleena,

We agree with your minor changes. Please finalize your response to the CR letter and comprehensive MedGuide submissions.

Thanks,
Bill

From: Sengupta, Debleena [mailto:Debleena.Sengupta@frx.com]
Sent: Friday, June 17, 2011 12:42 PM
To: Bender, William
Subject: RE: Celexa QT PI label and MedGuide

Dear Bill,

The team in essence agrees to the changes proposed by the Division. There are some minor changes that were included (attached).

PI

1. [REDACTED] (b) (4)
2. In 5.2, to be consistent, updated citalopram to Celexa
3. In 5.2, the word [REDACTED] (b) (4) was taken out because it was grammatically incorrect
4. In 7.8, language was updated to be consistent with the highlights section. Without [REDACTED] (b) (4) we feel it reads as if patients taking cimetidine should be taking Celexa. As opposed to if they happen to be taking Celexa, this should be the recommended dose

Medication Guide

1. Under [REDACTED] (b) (4) side effects, we would like to add Diarrhea back in, as it occurred at a frequency of 8% in the clinical trials
2. Under [REDACTED] (b) (4) side effects, we did have one question. We thought "Infections" might be too broad. Would it make more sense to have Respiratory Infections?

If the Division is ok with the changes, I will work on finalizing the response document and medguide amendment.

Regards,
Debleena

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Friday, June 03, 2011 4:33 PM

To: Sengupta, Debleena
Subject: Celexa QT PI label and MedGuide

Hi Debleena,

Hope all is well with you. Attached is our PI label regarding QT issues and the additional language in Section (b) (4) which is standard for all SSRIs. Also, please find our recommendations for the comprehensive MedGuide. If you agree with these changes, please respond to our 12-29-2010 CR letter (for the PI) and please send in amendment to the comprehensive Medguide.

Please contact me with any questions.

Thanks,
Bill

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

/s/

WILLIAM H BENDER
06/21/2011

From: Bender, William
Sent: Friday, June 03, 2011 4:33 PM
To: 'Sengupta, Debleena'
Subject: Celexa QT PI label and MedGuide

Attachments: Celexa-label 2011-05-25.doc; DRISK version Celexa-DNP proposed MG-May 18 2011.doc

Hi Debleena,

Hope all is well with you. Attached is our PI label regarding QT issues and the additional language in Section (b)(4) which is standard for all SSRIs. Also, please find our recommendations for the comprehensive MedGuide. If you agree with these changes, please respond to our 12-29-2010 CR letter (for the PI) and please send in amendment to the comprehensive Medguide.

Please contact me with any questions.

Thanks,
Bill



Celexa-label
11-05-25.doc (3)



DRISK version
lexa-DNP propo

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/s/

WILLIAM H BENDER
06/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>			
TO (<i>Office/Division</i>): Office of Surveillance and Epidemiology / Division of Risk Management (DRISK) Sarah Simon (OSE PM) Jodi Duckhorn (TL, Patient Labeling and Education)			FROM (<i>Name, Office/Division, and Phone Number of Requestor</i>): ODE 1 / Division of Psychiatry Products (DPP) Juliette Toure, PharmD (RPM)		
DATE August 31, 2009	IND NO.	NDA NO. Multiple, Please see below	TYPE OF DOCUMENT	DATE OF DOCUMENT Multiple, Please see below	
NAME OF DRUG		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Major Depressive Disorder (MDD)	DESIRED COMPLETION DATE October 31, 2009	
NAME OF FIRM: Multiple, Please see below.					
REASON FOR REQUEST					
I. GENERAL					
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY </div> <div style="width: 33%;"> <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT </div> <div style="width: 33%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): </div> </div>					
II. BIOMETRICS					
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG SAFETY					
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> NONCLINICAL		
COMMENTS / SPECIAL INSTRUCTIONS: DPP mandated class labeling Medication Guides (MG) in 2005, warning patients and caregivers of the increased risk of suicidality in children and adolescents, for all approved drugs to treat major depressive disorder (MDD). This class MG was further updated to include adults in 2007. DPP recently approved an efficacy supplement for Prozac in which the MG was revised from the class suicidality MG to a more comprehensive MG specific for Prozac. Our initiative is to have comprehensive MG for all modern drugs to treat MDD. Therefore, DPP issued supplement request letters on 4-16-09, requesting that sponsors submit a Prior Approval supplement providing for a comprehensive MG. DPP requests your input on the format and content of the Comprehensive Medication Guides submitted in response to our division's Prior Approval Supplement Request (PA SR) for drugs used to treat MDD. The PA SRs have been sent to the following sponsors and re: the respective NDAs:					

- Forest (NDAs 21-323/SLR-033 Lexapro tablet; 21-365/SLR-024 Lexapro solution; 20-822/SLR-038 Celexa tablet; 21-046/SLR-016 Celexa solution)
- GSK (NDAs 20-031/SLR-062 Paxil tablet; 20-710/SLR-026 Paxil solution; 20-936/SLR-040 Paxil CR tablet)
- Noven (NDA 21-299/SLR-024 Pexeva tablet)

(b) (4)

We've created an Eroom that contains all current submissions and can be accessed at the following link:
http://erom.fda.gov/eRoom/CDER/CDER-NPC/0_8f606

Prior to initiating your review of these Medication Guides, DPP would like to meet with DRISK to discuss a general approach on your review. Please contact the RPM, Juliette Toure, and inform her whom to invite to this meeting.

Attached to this consult, you'll find a list of NDAs and respective supplement numbers and a revised Prozac Med Guide that we propose to use as a template for the class.

Given that the regulatory due dates for these supplements are mid-November, we would appreciate your review of these labels being completed by the end of October.

Once the reviews are complete, please link the review to the respective NDA and also to the specific supplement in DARRTS.

SIGNATURE OF REQUESTOR Juliette Toure, PharmD	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Comprehensive Med Guide Summary

Sponsor	NDA#	Supp#	Drug Product	Submission Date	Received Date	Comments
Forest	21-323	033	Lexapro Tablet	14-May-09	14-May-09	
	21-365	024	Lexapro Solution	14-May-09	15-May-09	
	20-822	038	Celexa Tablet	15-May-09	18-May-09	
	21-046	016	Celexa Solution	15-May-09	18-May-09	
GSK	20-031	062	Paxil Tablet	15-May-09	15-May-09	
	20-710	026	Paxil Suspension	15-May-09	15-May-09	
	20-936	040	Paxil CR Tablet	15-May-09	15-May-09	
Noven	21-299	024	Pexeva Tablet	14-May-09	15-May-09	

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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(b) (4)

NDA-19839	SUPPL-72	PFIZER PHARMACEUTICA LS INC	ZOLOFT (SERTRALINE HCL) TABLET
NDA-20031	SUPPL-62	GLAXOSMITHKLIN E	PAXIL (PAROXETINE HCL) TABLETS

(b) (4)

NDA-20710	SUPPL-26	GLAXOSMITHKLIN E	PAXIL (PAROXETINE) ORAL SUSPENSION 10MG
NDA-20822	SUPPL-38	FOREST LABORATORIES INC	CELEXA
NDA-20936	SUPPL-40	GLAXOSMITHKLIN E	PAXIL(PAROXETINE HCL)CR TABS 12.5/25MG
NDA-20990	SUPPL-33	PFIZER PHARMACEUTICA LS INC	ZOLOFT(SERTRALINE HCL)20MG/ML ORALCONCEN
NDA-21046	SUPPL-16	FOREST LABORATORIES INC	CELEXA

(b) (4)

NDA-21299	SUPPL-24	NOVEN THERAPEUTICS LLC	PEXEVA 10,20,30 & 40MG. TABS
NDA-21323	SUPPL-33	FOREST LABORATORIES INC	LEXAPRO(ESCITALOPRAM OXALATE)5/10/20MG
NDA-21365	SUPPL-24	FOREST LABORATORIES INC	LEXAPRO (ESCITALOPRAM OXALATE 5MG/ML)

(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/

JULIETTE T TOURE

09/08/2009

THOMAS P LAUGHREN

09/08/2009

Toure, Juliette T

From: Toure, Juliette T
Sent: Monday, March 15, 2010 12:54 PM
To: 'Raposo, Maricarmen'
Subject: Comprehensive Med Guide - NDAs 20-822/S-038, 21-046/S-016, 21-323/S-033, 21-365/S-024

Attachments: SSRI Med Guide Template _11Mar2010.doc

Dear Ms. Raposo:

Please refer to your supplemental new drug application dated May 18, 2009, for Celexa Tablet (NDA 20-822/S-038) and Celexa Solution (NDA 21-046/S-016), and May 14, 2009, for Lexapro Tablet (NDA 21-323/S-033) and Lexapro Solution (NDA 21-365/S-024), providing for a comprehensive medication guide as requested in an Agency letter dated April 16, 2009.

The Division of Psychiatry Products has reviewed your submission, alongside others in the drug class indicated to treat Major Depressive Disorder (MDD). Because of the variability of the medication guide submissions across the drug class, the Division has developed a template for the comprehensive medication guide (attached). We request that you amend your prior approval supplement amendment, tailoring the template to information specific to your drug, including indication(s), side effects, contraindications, active and inactive ingredients, etc. Please submit a word version and track all changes as well as deviations from the template. As with any prior approval supplement, you will need to incorporate all previous revisions as reflected in the most recently approved package insert.

This amendment should be submitted within 30 days from the date of this letter. If you have any questions, you are welcome to email me directly.

Thanks,
Juliette



SSRI Med Guide
Template _11Mar...

Juliette Touré, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

Medication Guide
TRADENAME (phonetic spelling)
(established name)
(dosage formulations if there are more than one)

Read the Medication Guide that comes with TRADENAME before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about TRADENAME?

TRADENAME and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

- **TRADENAME and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment**.
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
 - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
 - Pay particular attention to such changes when TRADENAME is started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call a healthcare provider right away if you have 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 or panic attacks
- feeling agitated, restless, angry or irritable
- trouble sleeping
- acting aggressive or violent

- an increase in activity or talking from what is normal for you (mania)
- other unusual changes in behavior or mood

Tell your healthcare provider right away if you have any of the following symptoms of these serious side effects:

2. Serotonin Syndrome:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea

3. Severe allergic reactions:

- rash, itchy welts (hives) or blisters, alone or with fever or joint pain
- swelling of the face, tongue, eyes, or mouth
- trouble breathing

4. Abnormal bleeding: TRADENAME and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin, Jantoven), a non-steroidal anti-inflammatory drug (NSAID), or aspirin.

5. Seizures or convulsions

6. Manic episodes:

- abnormally increased energy
- severe trouble sleeping (insomnia)
- racing thoughts
- reckless behavior
- unusually grand ideas

7. Changes in appetite or weight. Children and adolescents should have height and weight monitored during treatment.

8. Low salt (sodium) levels in the blood

(hyponatremia). Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

Do not stop TRADENAME without first talking to your healthcare provider. Stopping TRADENAME may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or sleepy
- headache, sweating, nausea, dizziness
- electric shock-like sensations, tremor, confusion

TRADENAME is used to treat depression and other illnesses. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it.

What is TRADENAME?

TRADENAME is a prescription medicine used to treat: [\(insert indication\(s\) for the specific drug in the same format as below\)](#)

- Depression
- Obsessive Compulsive Disorder (OCD)
- Bulimia Nervosa
- Panic Disorder

Talk to your healthcare provider if you do not think that your condition is getting better with TRADENAME treatment.

Who should not take TRADENAME?

[\(Include contraindication\(s\) relevant to the drug\)](#)

Do not take TRADENAME if you:

- are allergic to (established name) or any of the ingredients in TRADENAME. See the end of this Medication Guide for a complete list of ingredients in TRADENAME.
- take an Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI.
 - Do not take an MAOI within 5 weeks of stopping TRADENAME.

- Do not start TRADENAME if you stopped taking an MAOI in the last 14 days (2 weeks).

People who take TRADENAME close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:

- high fever
- uncontrolled muscle spasms
- stiff muscles
- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)
- **take Mellaril (thioridazine). Do not take Mellaril within 5 weeks of stopping TRADENAME because this can cause serious heart rhythm problems or sudden death.**
- **take the antipsychotic medicine pimozide (Orap[®]) [\(adapt this statement to the drug\)](#)**

What should I tell my healthcare provider before taking TRADENAME?

Before starting TRADENAME, tell your healthcare provider if you:

- have a history of seizures (convulsions) or bipolar disorder (mania)
- have liver problems
- have diabetes. TRADENAME may cause problems with blood sugar control.
- have any other medical conditions
- are pregnant or plan to become pregnant. TRADENAME may harm your unborn baby.
- are breast-feeding or plan to breast-feed. Some TRADENAME may pass into your breast milk. You should not breast-feed while taking TRADENAME. Talk to your healthcare provider about the best way to feed your baby while taking TRADENAME. [\(adapt this statement to the drug\)](#)

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. TRADENAME and some

medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take TRADENAME with your other medicines. Do not start or stop any medicine while taking TRADENAME without talking to your healthcare provider first.

If you take TRADENAME, you should not take any other medicines that contain (established name) including: (insert TRADENAMES of drugs that have the same active ingredient).

How should I take TRADENAME?

- Take TRADENAME exactly as prescribed. Your healthcare provider may need to change the dose of TRADENAME until it is the right dose for you.
- TRADENAME may be taken with or without food.
- If you miss a dose of TRADENAME, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of TRADENAME at the same time.
- If you take too much TRADENAME, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking TRADENAME?

TRADENAME can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how TRADENAME affects you.

What are the possible side effects of TRADENAME?

TRADENAME may cause serious side effects, including:

- **See “What is the most important information I should know about TRADENAME?”**
- **Problems with blood sugar control.** People who have diabetes and take TRADENAME

may have problems with low blood sugar while taking TRADENAME. High blood sugar can happen when TRADENAME is stopped. Your healthcare provider may need to change the dose of your diabetes medicines when you start or stop taking TRADENAME.

• Feeling anxious or trouble sleeping

Common side effects in people who take TRADENAME include:

- unusual dreams
- sexual problems
- loss of appetite, diarrhea, indigestion, nausea, weakness, or dry mouth
- flu symptoms
- feeling too sleepy
- yawning
- sinusitis or sore throat
- nervousness, tremor, shaking, or sweating

Other side effects in children and adolescents include:

- increased thirst
- abnormal increase in muscle movement or agitation
- nose bleed
- urinating more often
- heavy menstrual periods
- slowed growth rate. Your child’s height and weight should be monitored during treatment with TRADENAME.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of TRADENAME. For more information, ask your healthcare provider or pharmacist.

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

How should I store TRADENAME? (adapt this section to the drug)

- Store TRADENAME at 59°F to 86°F (15°C to 30°C).
- Keep TRADENAME away from light.
- Keep TRADENAME bottle closed tightly.

Keep TRADENAME and all medicines out of the reach of children.

General information about TRADENAME

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRADENAME for a condition for which it was not prescribed. Do not give TRADENAME to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about TRADENAME. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about TRADENAME that is written for healthcare professionals.

For more information about TRADENAME call (insert 1-800 number) or go to www.TRADENAME.com.

What are the ingredients in TRADENAME?

Active ingredient: (established name)

Inactive ingredients:

- **(Formulation):** (insert inactive ingredients).

(Insert the name and address of the manufacturer, packer or distributor here.)

Revised Month Year

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