Celexa®
(citalopram hydrobromide)
Tablets/Oral Solution

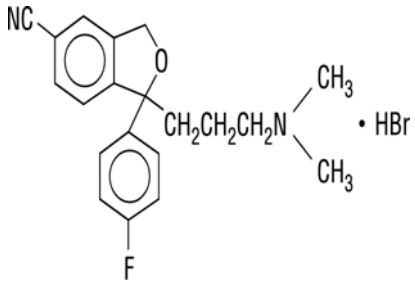
Rx Only

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 D_1 and D_2, α_1-, α_2-, and β-adrenergic, histamine H_1, 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 subjects ≥ 60 years old by 30% and 50%, respectively, whereas in a multiple-dose study they were increased by 23% and 30%, respectively. 20 mg/day is the maximum recommended dose for patients who are greater than 60 years of age (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**), 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/day is the maximum recommended dose for hepatically impaired patients (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**), due to the risk of QT prolongation.

CYP2C19 poor metabolizers – In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Celexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.

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 enzymes. However, *in vivo* data to address this question are limited.

CYP3A4 and CYP 2C19 inhibitors: Since CYP3A4 and CYP 2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of CYP3A4 (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 CYP3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. Celexa 20 mg/day is the maximum recommended dose in patients taking concomitant cimetidine or another CYP2C19 inhibitor, because of the risk of QT prolongation (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

CYP2D6 Inhibitors: Coadministration of a drug that inhibits CYP2D6 with Celexa is unlikely to have clinically significant effects on citalopram metabolism, based on the study results in CYP2D6 poor metabolizers.

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

The use of MAOIs intended to treat psychiatric disorders with Celexa or within 14 days of stopping treatment with Celexa is contraindicated because of an increased risk of serotonin syndrome. The use of Celexa within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (see **WARNINGS and DOSAGE and ADMINISTRATION**).

Starting Celexa in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome (see **WARNINGS and DOSAGE AND ADMINISTRATION**).

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 QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes (TdP), ventricular tachycardia, and sudden death, all of which

have been observed in postmarketing reports for citalopram.

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.

Because of the risk of QTc prolongation at higher citalopram doses, it is recommended that citalopram should not be given at doses above 40 mg/day.

It is recommended that citalopram should not be used in patients with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure. Citalopram should also not be used in patients who are taking other drugs that prolong the QTc interval. Such drugs include Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).

The citalopram dose should be limited in certain populations. The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, since higher citalopram exposures would be expected. The maximum dose should also be limited to 20 mg/day in patients with hepatic impairment and in patients who are greater than 60 years of age because of expected higher exposures.

Electrolyte and/or ECG monitoring is recommended in certain circumstances. Patients being considered for citalopram treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QTc prolongation and arrhythmia, and should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients for whom citalopram use is not recommended (see above), but, nevertheless, considered essential. These include those patients with the cardiac conditions noted above, and those taking other drugs that may prolong the QTc interval.

Citalopram should be discontinued in patients who are found to have persistent QTc measurements >500 ms. If patients taking citalopram experience symptoms that could indicate

the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

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.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Celexa, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, trytophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Celexa with MAOIs intended to treat psychiatric disorders is contraindicated. Celexa should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Celexa. Celexa should be discontinued before initiating treatment with the MAOI (see **CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION**).

If concomitant use of Celexa with other serotonergic drugs including, triptans, tricyclic

antidepressants, fentanyl, lithium, tramadol, buspirone, trytophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome particularly during treatment initiation and dose increases.

Treatment with Celexa and any concomitant serotonergic agents 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, citalopram use should be avoided in patients with certain cardiac conditions, and ECG monitoring is advised if Celexa must be used in such

patients. Electrolytes should be monitored in treating patients with diseases or conditions that cause hypokalemia or hypomagnesemia. (see **WARNINGS**).

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.

Drug Interactions

Serotonergic Drugs: See **CONTRAINDICATIONS**, **WARNINGS, and DOSAGE AND ADMINISTRATION.**

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**, **WARNINGS and DOSAGE AND ADMINISTRATION**.

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 **WARNINGS** and **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.

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

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 $\geq$ 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 serotonin and norepinephrine reuptake inhibitors (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: Serotonin Syndrome**).

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1- 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including Celexa) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with Celexa, the physician should carefully consider both the potential risks of taking an SSRl, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis (see **DOSAGE AND ADMINISTRATION**).

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 subjects $\geq$ 60 years of age as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively (see **CLINICAL PHARMACOLOGY**).

20 mg/day is the maximum recommended dose for patients who are greater than 60 years of age (see **WARNINGS** and **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**	**Placebo**
	(N=1063)	**(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 ≥ Celexa: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.

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

[2]Primarily ejaculatory delay.

[3]Denominator 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 pec toris, 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:* hayfever.

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 at an interval 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 maximum recommended dose for patients who are greater than 60 years of age, patients with hepatic impairment, and for CYP2C19 poor metabolizers or those patients taking cimetidine or another CYP2C19 inhibitor. (see **WARNINGS**)

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.

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 a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with Celexa. Conversely, at least 14 days should be allowed after stopping Celexa before starting an MAOI intended to treat psychiatric disorders (see **CONTRAINDICATIONS**).

Use of Celexa with Other MAOIs, Such as Linezolid or Methylene Blue

Do not start Celexa in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered (see **CONTRAINDICATIONS)**.

In some cases, a patient already receiving Celexa therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, Celexa should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Celexa may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see **WARNINGS**).

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with Celexa is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see **WARNINGS**).

HOW SUPPLIED

Tablets:

10 mg	Bottle of 100	NDC # 0456-4010-01

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
10 x 10 Unit Dose		NDC # 0456-4020-63

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
10 x 10 Unit Dose		NDC # 0456-4040-63

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

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/m^2 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/m^2 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/m^2 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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Rev. Month Year

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. 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.

- If you 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 2 weeks of stopping Celexa unless directed to do so by your physician.
- Do not start Celexa if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

  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, crosscarmellose 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: Month Year

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St. Louis, MO 63045 USA

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

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

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

----------RECENT MAJOR CHANGES----------
- Dosage and Administration (2.5, 2.6) MM/YYYY
- Contraindications (4.1) MM/YYYY
- Warnings and Precautions (5.2) MM/YYYY

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

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

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

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

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

----------CONTRAINDICATIONS----------
- Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with Lexapro or within 14 days of stopping treatment with Lexapro. Do not use Lexapro within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start Lexapro in a patient who is being treated with linezolid or intravenous methylene blue (4.1).
- Pimozide: Do not use concomitantly (4.2).
- Known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients (4.3).

----------WARNINGS AND PRECAUTIONS----------
- Clinical Worsening/Suicide Risk: Monitor for clinical worsening, suicidality and unusual change in behavior, especially, during the initial few months of therapy or at times of dose changes (5.1).
- Serotonin Syndrome: Serotonin syndrome has been reported with SSRIs and SNRIs, including Lexapro, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort). If such symptoms occur, discontinue Lexapro and initiate supportive treatment. If concomitant use of Lexapro with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2).
- Discontinuation of Treatment with Lexapro: A gradual reduction in dose rather than abrupt cessation is recommended whenever possible (5.3).
- Seizures: Prescribe with care in patients with a history of seizure (5.4).
- Activation of Mania/Hypomania: Use cautiously in patients with a history of mania (5.5).
- Hyponatremia: Can occur in association with SIADH (5.6).
- Abnormal Bleeding: Use caution in concomitant use with NSAIDs, aspirin, warfarin or other drugs that affect coagulation (5.7).
- Interference with Cognitive and Motor Performance: Use caution when operating machinery (5.8).
- Use in Patients with Concomitant Illness: Use caution in patients with diseases or conditions that produce altered metabolism or hemodynamic responses (5.9).

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

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

----------DRUG INTERACTIONS----------
Concomitant use with SSRIs, SNRIs or Tryptophan is not recommended (7.2).
Use caution when concomitant use with drugs that affect Hemostasis (NSAIDs, Aspirin, Warfarin) (7.6).

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: Month Year

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

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

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

1.2 Generalized Anxiety Disorder

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

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

2 DOSAGE AND ADMINISTRATION

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

2.1 Major Depressive Disorder

Initial Treatment

Adolescents

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

Adults

The recommended dose of Lexapro is 10 mg once daily. A fixed-dose trial of Lexapro demonstrated the effectiveness of both 10 mg and 20 mg of Lexapro, but failed to demonstrate a greater benefit of 20 mg over 10 mg [*see Clinical Studies (14.1)*]. If the dose is increased to 20 mg, this should occur after a minimum of one week.

Maintenance Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of continuing Lexapro 10 or 20 mg/day in adults patients with major depressive disorder who responded while taking Lexapro during an 8-week, acute-treatment phase demonstrated a benefit of such maintenance treatment [*see Clinical Studies (14.1*)]. Nevertheless, the physician who elects to use

Lexapro for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.2 Generalized Anxiety Disorder

Initial Treatment

Adults

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

Maintenance Treatment

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

2.3 Special Populations

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

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

2.4 Discontinuation of Treatment with Lexapro

Symptoms associated with discontinuation of Lexapro and other SSRIs and SNRIs have been reported [*see Warnings and Precautions (5.3)*]. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

2.5 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with Lexapro. Conversely, at least 14 days should be allowed after stopping Lexapro before starting an MAOI intended to treat psychiatric disorders [*see Contraindications (4.1)*].

2.6 Use of Lexapro with Other MAOIs such as Linezolid or Methylene Blue

Do not start Lexapro in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4.1)]*.

In some cases, a patient already receiving Lexapro therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, Lexapro should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Lexapro may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.2)]*.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with Lexapro is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

3.1 Tablets

Lexapro tablets are film-coated, round tablets containing escitalopram oxalate in strengths equivalent to 5 mg, 10 mg and 20 mg escitalopram base. The 10 and 20 mg tablets are scored. Imprinted with "FL" on one side and either "5", "10", or "20" on the other side according to their respective strengths.

3.2 Oral Solution

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

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs intended to treat psychiatric disorders with Lexapro or within 14 days of stopping treatment with Lexapro is contraindicated because of an increased risk of serotonin syndrome. The use of Lexapro within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated [*see Dosage and Administration (2.5), and Warnings and Precautions (5.2)*].

Starting Lexapro in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome [*see Dosage and Administration (2.6), and Warnings and Precautions (5.2)*].

4.2 Pimozide

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

4.3 Hypersensitivity to escitalopram or citalopram

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

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

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

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

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

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

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

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

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

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

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

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

Screening Patients for Bipolar Disorder

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

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Lexapro, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl,

lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination) seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Lexapro with MAOIs intended to treat psychiatric disorders is contraindicated. Lexapro should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Lexapro. Lexapro should be discontinued before initiating treatment with the MAOI [*see Contraindications (4.1) and Dosage and Administration (2.5 and 2.6)*].

If concomitant use of Lexapro with other serotonergic drugs including, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Lexapro and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Discontinuation of Treatment with Lexapro

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

Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [*see Dosage and Administration (2.4)*].

5.4 Seizures

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

5.5 Activation of Mania/Hypomania

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

5.6 Hyponatremia

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

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

5.7 Abnormal Bleeding

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

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

5.8 Interference with Cognitive and Motor Performance

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

5.9 Use in Patients with Concomitant Illness

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

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

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day [*see Dosage and Administration (2.3)*].

Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients [*see Dosage and Administration (2.3)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Clinical Trial Data Sources
Pediatrics (6 -17 years)
Adverse events were collected in 576 pediatric patients (286 Lexapro, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Lexapro in pediatric patients less than 12 years of age has not been established.

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

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

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

Adverse Events Associated with Discontinuation of Treatment

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

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

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

Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials

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

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

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

TABLE 2 Treatment-Emergent Adverse Reactions observed with a frequency of ≥ 2% and greater than placebo for Major Depressive Disorder		
Adverse Reaction	**Lexapro (N=715)**	**Placebo (N=592)**
	%	**%**
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

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

Generalized Anxiety Disorder

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

Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

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

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=182 Lexapro; N=195 placebo).
[3]Denominator used was for females only (N=247 Lexapro; N=232 placebo).

Dose Dependency of Adverse Reactions

The potential dose dependency of common adverse reactions (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse reactions in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse reactions that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group.

TABLE 4			
Incidence of Common Adverse Reactions in Patients with Major Depressive Disorder			
Adverse Reaction	**Placebo**	**10 mg/day**	**20 mg/day**
	(N=311)	**Lexapro**	**Lexapro**
		(N=310)	**(N=125)**
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

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

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

TABLE 5		
Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials		
Adverse Event	**Lexapro**	**Placebo**
	In Males Only	
	(N=407)	(N=383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	3%	1%
Anorgasmia	3%	<1%

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

Priapism has been reported with all SSRIs.

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

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

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

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

ECG Changes
Electrocardiograms from Lexapro (N=625) and placebo (N=527) 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). None of the patients in the Lexapro group had a QTcF interval >500 msec or a prolongation >60 msec compared to 0.2% of patients in the placebo group. The incidence of tachycardic outliers was 0.2% in the Lexapro and the placebo group. The incidence of bradycardic outliers was 0.5% in the Lexapro group and 0.2% in the placebo group.

QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 113 healthy subjects. The maximum mean (95% upper confidence bound) difference from placebo arm were 4.5 (6.4) and 10.7 (12.7) msec for 10 mg and supratherapeutic 30 mg escitalopram given once daily, respectively. Based on the established exposure-response relationship, the predicted QTcF change from placebo arm (95% confidence interval) under the C_{max} for the dose of 20 mg is 6.6 (7.9) msec. Escitalopram 30 mg given once daily resulted in mean C_{max} of 1.7-fold higher than the mean C_{max} for the maximum recommended therapeutic dose at steady state (20 mg). The exposure under supratherapeutic 30 mg dose is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.

Other Reactions Observed During the Premarketing Evaluation of Lexapro
Following is a list of treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. The listing does not include those events already listed in **Tables 2 & 3**, those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Events are categorized by body system. Events of major clinical importance are described in the Warnings and Precautions section (5).

Cardiovascular - hypertension, palpitation.

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

Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis.

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

Metabolic and Nutritional Disorders - increased weight.

Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness.

Psychiatric Disorders - appetite increased, concentration impaired, irritability.

Reproductive Disorders/Female - menstrual cramps, menstrual disorder.

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

Skin and Appendages Disorders - rash.

Special Senses - vision blurred, tinnitus.

Urinary System Disorders - urinary frequency, urinary tract infection.

6.2 Post-Marketing Experience

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

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

Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia.
Ear and labyrinth disorders: vertigo
Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH.
Eye Disorders: diplopia, glaucoma, mydriasis, visual disturbance.
Gastrointestinal Disorder: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage.
General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise.
Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis.
Immune System Disorders: allergic reaction, anaphylaxis.
Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased.
Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia.
Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis.
Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor.
Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion.
Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency.
Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention.
Reproductive System and Breast Disorders: menorrhagia, priapism.
Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn.
Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria.
Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors (MAOIs)

[See Dosage and Administration (2.5 and 2.6), Contraindications (4.1) and Warnings and Precautions (5.2)].

7.2 Serotonergic Drugs

[See Dosage and Administration (2.5 and 2.6), Contraindications (4.1) and Warnings and Precautions (5.2)].

7.3 Triptans

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

7.4 CNS Drugs

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

7.5 Alcohol

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

7.6 Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Lexapro is initiated or discontinued.

7.7 Cimetidine

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

7.8 Digoxin

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

7.9 Lithium

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

7.10 Pimozide and Celexa

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

7.11 Sumatriptan

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

7.12 Theophylline

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

7.13 Warfarin

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

7.14 Carbamazepine

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

7.15 Triazolam

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

7.16 Ketoconazole

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

7.17 Ritonavir

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

7.18 CYP3A4 and -2C19 Inhibitors

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

7.19 Drugs Metabolized by Cytochrome P4502D6

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

7.20 Metoprolol

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

7.21 Electroconvulsive Therapy (ECT)

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

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

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

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

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

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

Pregnancy-Nonteratogenic Effects

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

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 - 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including Lexapro) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with Lexapro, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis [see Dosage and Administration (2.1.)].

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

Decrease 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.

8.5 Geriatric Use

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

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

In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged [*see Clinical Pharmacology (12.3)*]. 10 mg/day is the recommended dose for elderly patients [*see Dosage and Administration (2.3)*].

Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse and Dependence

Physical and Psychological Dependence

Animal studies suggest that the abuse liability of racemic citalopram is low. Lexapro has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Lexapro did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Lexapro patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

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

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

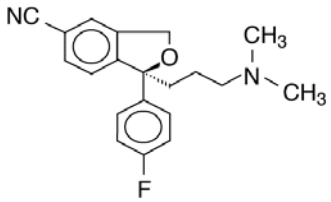
10.2 Management of Overdose

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

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

11 DESCRIPTION

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



•$C_2H_2O_4$

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

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

Absorption and Distribution

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

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

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

Metabolism and Elimination

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

Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the concentration of the escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT

and S-DDCT also have no or very low affinity for serotonergic (5-HT_{1-7}) or other receptors including alpha- and beta-adrenergic, dopamine (D_{1-5}), histamine (H_{1-3}), muscarinic (M_{1-5}), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na^+, K^+, Cl^-, and Ca^{++} channels.

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

Population Subgroups

Age

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

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

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

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

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

Drug-Drug Interactions

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

Retinal Changes in Rats

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

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

Cardiovascular Changes in Dogs

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

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

Adolescents

The efficacy of Lexapro as an acute treatment for major depressive disorder in adolescent patients was established in an 8-week, flexible-dose, placebo-controlled study that compared Lexapro 10-20 mg/day to placebo in outpatients 12 to 17 years of age inclusive who met DSM-IV criteria for major depressive disorder. The primary outcome was change from baseline to endpoint in the Children's Depression Rating Scale - Revised (CDRS-R). In this study, Lexapro showed statistically significant greater mean improvement compared to placebo on the CDRS-R.

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

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

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

Adults

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

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

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

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

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

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

14.2 Generalized Anxiety Disorder

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Tablets

5 mg Tablets:
Bottle of 100 NDC # 0456-2005-01
White to off-white, round, non-scored, film-coated. Imprint "FL" on one side of the tablet and "5" on the other side.

10 mg Tablets:
Bottle of 100 NDC # 0456-2010-01
10 x 10 Unit Dose NDC # 0456-2010-63
White to off-white, round, scored, film-coated. Imprint on scored side with "F" on the left side and "L" on the right side. Imprint on the non-scored side with "10".

20 mg Tablets:
Bottle of 100 NDC # 0456-2020-01
10 x 10 Unit Dose NDC # 0456-2020-63
White to off-white, round, scored, film-coated. Imprint on scored side with "F" on the left side and "L" on the right side. Imprint on the non-scored side with "20".

16.2 Oral Solution

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide

17.1 Information for Patients

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

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

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

Clinical Worsening and Suicide Risk

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

Serotonin Syndrome
Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of **Lexapro** with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol tryptophan, buspirone and St. John's Wort, and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid) [*see Warnings and Precautions (5.2)*].

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

Concomitant Medications
Since escitalopram is the active isomer of racemic citalopram (Celexa), the two agents should not be coadministered. Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.

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

Interference with Psychomotor Performance
Because psychoactive drugs may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities.

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

Pregnancy and Breast Feeding
Patients should be advised to notify their physician if they

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

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

17.2 FDA-Approved Medication Guide

Medication Guide

Lexapro® (leks-a-pro)
(escitalopram oxalate)
Tablets/Oral Solution

Read the Medication Guide that comes with Lexapro 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 Lexapro?

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

1. Suicidal thoughts or actions:

- **Lexapro 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 Lexapro 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. Lexapro may be associated with these serious side effects:

2. Serotonin Syndrome. 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

3. 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

4. Abnormal bleeding: Lexapro 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.

5. Seizures or convulsions

6. 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

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. 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 Lexapro without first talking to your healthcare provider. Stopping Lexapro 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 Lexapro?

Lexapro 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. Lexapro is also used to treat:
- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)

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

Who should not take Lexapro?

Do not take Lexapro if you:
- are allergic to escitalopram oxalate or citalopram hydrobromide or any of the ingredients in Lexapro. See the end of this Medication Guide for a complete list of ingredients in Lexapro.
- If you 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 2 weeks of stopping Lexapro unless directed to do so by your physician.
- Do not start Lexapro if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

People who take Lexapro 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 taking this drug with Lexapro can cause serious heart problems.**

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

Before starting Lexapro, tell your healthcare provider if you:
- Are taking certain drugs such as:
  - 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 Lexapro 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 Lexapro may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking Lexapro.

Tell your healthcare provider about all the medicines **that you take,** including prescription and non-prescription medicines, vitamins, and herbal supplements. Lexapro 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 Lexapro with your other medicines. Do not start or stop any medicine while taking Lexapro without talking to your healthcare provider first.

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

How should I take Lexapro?

- Take Lexapro exactly as prescribed. Your healthcare provider may need to change the dose of Lexapro until it is the right dose for you.
- Lexapro may be taken with or without food.
- If you miss a dose of Lexapro, 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 Lexapro at the same time.
- If you take too much Lexapro, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking Lexapro?

Lexapro 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 Lexapro affects you. Do not drink alcohol while using Lexapro.

What are the possible side effects of Lexapro?

Lexapro may cause serious side effects, including all of those described in the section entitled "What is the most important information I should know about Lexapro?"

Common possible side effects in people who take Lexapro include**:**
- Nausea
- Sleepiness
- Weakness
- Dizziness
- Feeling anxious
- Trouble sleeping
- Sexual problems
- Sweating
- Shaking
- Not feeling hungry
- Dry mouth
- Constipation
- Infection
- Yawning

Other side effects in children and adolescents include:
- increased thirst
- abnormal increase in muscle movement or agitation
- nose bleed
- difficult urination
- heavy menstrual periods
- possible slowed growth rate and weight change. Your child's height and weight should be monitored during treatment with Lexapro.

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 Lexapro. 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 Lexapro?

- Store Lexapro at 25°C (77°F); excursions permitted to 15 - 30°C (59-86°F).
- Keep Lexapro bottle closed tightly.

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

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

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

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

What are the ingredients in Lexapro?

Active ingredient: escitalopram oxalate
Inactive ingredients:

- **Tablets**: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, and polyethylene glycol.
- **Oral Solution:** sorbitol, purified water, citric acid, sodium citrate, malic acid, glycerin, propylene glycol, methylparaben, propylparaben, and natural peppermint flavor.

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