



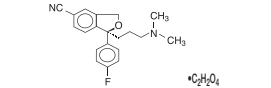
Lexapro®
(escitalopram oxalate)
TABLETS/ORAL SOLUTION
Rx Only

Suicidality in Children and Adolescents
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. (See Warnings and Precautions: Pediatric Use.)

Poolled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD or other psychiatric disorders (a total of 24 trials involving over 4000 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, while the placebo risk is 2%. No suicides occurred in these trials.

DESCRIPTION

Lexapro® (escitalopram oxalate) is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the *S*-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated *S*-(+)-1-(3-[(*S*)-ethylamino]propyl)-*cis*-(4-thiophenyl)-*p*-phthalancarbon oxalate with the following structural formula:



The molecular formula is C₁₉H₂₁NO₄ · C₂H₂O₄ and the molecular weight is 414.4. 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: lact, croscarmellose sodium, microcrystalline cellulose/croscarmellose sodium 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.

CLINICAL PHARMACOLOGY
Pharmacodynamics
The mechanism of antidepressant action of escitalopram, the *S*-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). In vitro and in vivo studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100-fold more potent than the *R*-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{2D}), muscarinic (M₁₋₄), and benzodiazepine receptors. Escitalopram also does not bind to, or has low affinity for, various ion channels including Na⁺, K⁺, Ca²⁺, and Ca²⁺ channels. Antagonism of muscarinic, histaminergic, and beta-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular side effects of other psychotropic drugs.

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Bioavailability 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 escitalopram 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 administration of escitalopram, the fraction of drug recovered in the urine as escitalopram and *S*-dimethylcitalopram (*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*-dimethylcitalopram (*S*-DCT). 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*-DCT was not detectable in most subjects. In two studies show that escitalopram is at least 7 and 27 times more potent than *S*-DCT and *S*-DCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant activity of escitalopram. *S*-DCT and *S*-DCT also have no or very low affinity for serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{2D}), histamine (H₁₋₃), muscarinic (M₁₋₄), and benzodiazepine receptors. *S*-DCT and *S*-DCT also do not bind to various ion channels including Na⁺, K⁺, Ca²⁺, and Ca²⁺ channels. In *in vitro* studies using human liver microsomes, the primary CYP2A6 and CYP2C19 are the primary isozymes involved in the *N*-demethylation of escitalopram.

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

Gender - In a multiple-dose study of escitalopram (10 mg/day for 9 weeks) in 18 male (8 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max}, and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Reduced hepatic function - Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is the recommended dose of escitalopram for most hepatically impaired patients (see DOSAGE AND ADMINISTRATION). Impaired 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 *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 SSRI inhibitory effect and a modest 20% inhibitory effect. See Drug Interactions under PRECAUTIONS for more detailed information on available drug interaction data.

Clinical Efficacy Trials
Major Depressive Disorder
The efficacy of Lexapro as a treatment for major depressive disorder was established in three, 8-week, placebo-controlled studies conducted in outpatients between 18 and 65 years of age who met DSM-IV criteria for major depressive disorder. The primary outcome in all three studies was change from baseline to endpoint in the Montgomery-Åsberg Depression Rating Scale (MADRS). A fixed-dose study compared 10 mg/day Lexapro, 20 mg/day Lexapro to placebo and 40 mg/day citalopram. The 10 mg/day and 20 mg/day Lexapro treatment groups showed significantly greater mean improvement compared to placebo on the MADRS. The 10 mg and 20 mg Lexapro groups were similar on this outcome measure.

In a second fixed-dose study of 10 mg/day Lexapro and placebo, the 10 mg/day Lexapro treatment group showed significantly greater mean improvement compared to placebo on the MADRS. In a flexible-dose study, comparing Lexapro, titrated between 10 and 40 mg/day, to placebo and citalopram, titrated between 20 and 40 mg/day, the Lexapro treatment group showed significantly greater mean improvement compared to placebo on the MADRS. In a flexible-dose study, comparing Lexapro, titrated between 10 and 20 mg/day, to placebo and citalopram, titrated between 20 and 40 mg/day, the Lexapro treatment group showed significantly greater mean improvement compared to placebo on the MADRS. Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

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

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

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

INDICATIONS AND USAGE
Major Depressive Disorder
Lexapro (escitalopram) is indicated for the treatment of major depressive disorder. The efficacy of Lexapro in the treatment of major depressive disorder was established in three, 8-week, placebo-controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY). A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypnosis, decreased energy, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. The efficacy of Lexapro in hospitalized patients with major depressive disorders has not been adequately studied.

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

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

The efficacy of Lexapro was established in three, 8-week, placebo-controlled trials in patients with GAD (see CLINICAL PHARMACOLOGY). Generalized Anxiety Disorder (DSM-IV) is characterized by excessive, free anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. The efficacy of Lexapro in the long-term treatment of GAD, that is, for more than 8 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Lexapro for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS). Concomitant use in patients taking pimozide is contraindicated (see Drug Interactions - Pimozide and Citalopram). Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or to any of the inactive ingredients in Lexapro.

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. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Poolled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4000 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, and a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (suicidic obsessive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. All pediatric patients being treated with antidepressants for any indication should be 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. Such observation would generally include at least weekly visits to the prescriber for at least the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, 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 are concerns 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 under DOSAGE AND ADMINISTRATION - Discontinuation of Treatment with Lexapro, for a description of the risks of discontinuation of Lexapro).

Families and caregivers of pediatric 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, hostility, aggressiveness, or 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 Lexapro should be written for the smallest quantity of tablets consistent with good patient management practices to minimize the potential for abuse. Families and caregivers of adults being treated for depression should be similarly advised. **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 manic or depressive episodes. Therefore, it is important that Lexapro is not approved for use in treating bipolar depression.

Prophylaxis for Interaction with Monoamine Oxidase Inhibitors
In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serotonin syndrome, sensory disturbances (e.g., paresthesias such as electric mylonias, autonomic instability with possible rapid fluctuations of vital signs), and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral activation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed between discontinuation of an MAOI and starting Lexapro. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.

PRECAUTIONS
General
Discontinuation of Treatment with Lexapro
During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when used at higher doses, including the following: dizziness, headache, flu-like symptoms, nausea, vomiting, diarrhea, and changes in vision. These events are generally self-limiting, and have been reported in patients with various psychiatric disorders. 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. It is advisable to monitor closely 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).

Algorism Bleeding
Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see Drug Interactions). Although these

studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation.

Hypomania
Cases of hypomania and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Lexapro treatment. All patients with these events have recovered with discontinuation of escitalopram and/or medical intervention. Hypomania and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder.

Activation of Mania/Hypomania
In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in one of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania.

Seizures
Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies of Lexapro'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.

Adults 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 does not affect their ability to engage in such activities.

Use in Patients with Concomitant Illness
Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in these subjects is 5 mg once daily (see DOSAGE AND ADMINISTRATION). Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

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

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

Patients should be told that, although Lexapro has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Lexapro and alcohol in depressed patients is not advised. Patients should be made aware that escitalopram is the active isomer of *cis*-citalopram (hydrochloride) and that the two medications should not be taken concomitantly. Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.

Patients should be cautioned about the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breastfeeding or intend to breastfeed, as it is not known whether Lexapro is excreted in milk.

While patients may notice improvement with Lexapro 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 Lexapro and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers 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 before they begin to take Lexapro, and they should be encouraged to ask questions if they do not understand. 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.

Warnings and Precautions: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or 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 observe 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 a worsening of depression and/or the emergence of suicidal impulses and indicate a need for very close monitoring and possibly changes in the medication.

Laboratory Tests
There are no specific laboratory tests recommended. **Concomitant Administration with Racemic Citalopram**
Concomitant Administration with Racemic Citalopram - Since escitalopram is the active isomer of racemic citalopram, the two agents should not be coadministered. **Drug Interactions**
CNS Drugs - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

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

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

Cimetidine - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 59%, respectively. The clinical significance of these findings is unknown. **Digoxin** - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium - Co-administration of racemic citalopram (40 mg/day for 10 days) and lithium (90 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 during the concurrent use of these agents.

Pimozide and Citalopram - In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg once 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 pharmacokinetic interaction is not known.

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

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

Ketocoazole - Combined administration of racemic citalopram (40 mg/day for 14 days) and ketocoazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} of escitalopram by 21% and 17%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

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

5-HT_{2A} and 5-HT_{2C} Inhibitors - In *in vitro* studies indicated that CYP3A4 and 5-HT_{2A} 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 affect escitalopram clearance.

Drugs Metabolized by Cytochrome P4502D6 - In *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 escitalopram. Subsequent 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 tri-cyclic 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.

Carbamazepine
Drugs Metabolized by Cytochrome P4502D6 - In *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 escitalopram. Subsequent 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 tri-cyclic 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 combination of escitalopram and drugs metabolized by CYP2D6.

Metoprolol - Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{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 effect on blood pressure or heart rate. **Electroconvulsive Therapy (ECT)** - There are no clinical studies of the combined use of ECT and escitalopram.

Carbamazepine, Valproic Acid, and Phenytoin
Carbamazepine
Escitalopram was administered in the diet to NR1R/BOM strain mice and COBS WJ 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 no evidence of small intestine adenomas in rats receiving 8 or 24 mg/kg/day of racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis
Escitalopram 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 mice prior to and throughout mating and gestation at doses of 52, 82, and 127 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day.

Pregnancy
Pregnancy Category C
In a rat embryo-fetal development study, oral administration of escitalopram (5, 112, or 152 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated

Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be



3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider **right away** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider.

Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac™) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac™), sertraline (Zoloft™), fluvoxamine, and clomipramine (Anafranil™).

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

* Prozac® is a registered trademark of Eli Lilly and Company

* Zoloft® is a registered trademark of Pfizer Pharmaceuticals

* Anafranil® is a registered trademark of Mallinckrodt Inc.

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

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/m²] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild to moderate mortality and growth retardation were noted at 48 mg/kg/day of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m² basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m² basis).

When female rats were treated with escitalopram (5, 12, 24, or 48 mg/kg/day) during pregnancy and during 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/m² basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m² basis.

In animal reproductive 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, 64, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryofetal 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, adverse effects on fetal development were observed at some doses of racemic citalopram of up to 18 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-Nonteratologic Effects
Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a withdrawal syndrome. It is not clear whether these features, if they occur, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

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

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

Nursing Mothers
Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss. In one case, the infant was 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 Lexapro therapy should take into account the risks of citalopram exposure for the infant and the benefits of Lexapro treatment for the mother.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). One placebo-controlled trial in 264 pediatric patients with MDD has been conducted with Lexapro, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Lexapro in a child or adolescent must balance the potential risks with the clinical need.

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. There were no clinically important differences in these trials between patients in these trials receiving daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out.

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

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

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

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

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

Adverse Events Associated with Discontinuation of Treatment
Major Depressive Disorder
Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of

discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients).

Generalized Anxiety Disorder
Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 0% discontinued treatment due to an adverse event as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%).

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

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

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

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

| Body System / Adverse Event | (Percentage of Patients Reporting Event) | |
|-------------------------------------|--|-----------------|
| | Placebo (N=715) | Lexapro (N=592) |
| Psychiatric Disorders | | |
| Insomnia | 5% | 14% |
| Diarrhea | 4% | 7% |
| Dry Mouth | 3% | 4% |
| Somnolence | 1% | 9% |
| Dizziness | <1% | 3% |
| Sweating Increased | 2% | 6% |
| Constipation | 1% | 3% |
| Fatigue | 2% | 2% |
| Indigestion | 1% | 2% |
| Respiratory System Disorders | | |
| Rhinitis | 3% | 4% |
| Sinusitis | 5% | 2% |
| Urogenital | | |
| Ejaculation Disorder ^{b,2} | 9% | <1% |
| Impotence ^b | 3% | <1% |
| Neurologic Disorders | | |
| Headache | 9% | 4% |
| Vertigo | 3% | 1% |
| Ataxia | 3% | 1% |
| Abnormalities in Laboratory Tests | | |
| Leukopenia | 2% | 1% |
| Neutropenia | 2% | 1% |
| Thrombocytopenia | 2% | 1% |
| Other Events | | |
| Fluorescence-like Symptoms | 5% | 4% |
| Fatigue | 5% | 2% |
| Psychiatric Disorders | | |
| Insomnia | 9% | 4% |
| Somnolence | 6% | 2% |
| Appetite Decreased | 3% | 1% |
| Libido Decreased | 3% | 1% |

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

^b Primarily ejaculatory delay.

² Denominator used was for males only (N=225; Lexapro; N=183 placebo).

³ Denominator used was for females only (N=40; Lexapro; N=404 placebo).

Generalized Anxiety Disorder

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

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

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

| Body System / Adverse Event | (Percentage of Patients Reporting Event) | |
|---|--|-----------------|
| | Placebo (N=429) | Lexapro (N=427) |
| Psychiatric 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% |
| Headache | 3% | 2% |
| Vomiting | 3% | 1% |
| Abdominal Pain | 2% | 1% |
| Fatulence | 2% | 1% |
| Toothache | 2% | 1% |
| General | | |
| Fatigue | 8% | 2% |
| Influenza-like Symptoms | 5% | 4% |
| Musculoskeletal | | |
| Neck/Shoulder Pain | 3% | 1% |

Psychiatric Disorders

Somnolence

Urogenital

Dose Dependency of Adverse Events

The potential dose-dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro group) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg Lexapro-treated patients was greater (68%). Table 3 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group.

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

| Adverse Event | Placebo (N=511) | 10 mg/day Lexapro (N=510) | 20 mg/day Lexapro (N=125) |
|--------------------|-----------------|---------------------------|---------------------------|
| Insomnia | 4% | 7% | 14% |
| Diarrhea | 5% | 6% | 14% |
| Dry Mouth | 3% | 4% | 9% |
| Somnolence | 1% | 4% | 9% |
| Dizziness | <1% | 3% | 7% |
| Sweating Increased | 2% | 4% | 8% |
| Constipation | 1% | 3% | 6% |
| Fatigue | 2% | 2% | 6% |
| Indigestion | 1% | 2% | 6% |

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

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

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

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

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

| Adverse Event | Lexapro | | Placebo |
|--|---------------|-----------------|---------|
| | In Males Only | In Females Only | |
| Ejaculation Disorder (primarily ejaculatory delay) | 12% | 1% | 2% |
| Libido Decreased | 6% | 2% | 1% |
| Impotence | 2% | <1% | 1% |

Other Events

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

Prigrip 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.

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

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

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

ECG Changes
Electrocardiograms from Lexapro (N=625), racemic citalopram (N=561), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes in these variables. These analyses revealed (1) a decrease in heart rate of 2.3 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities.

Other Events Observed During the Premarketing Evaluation of Lexapro
Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its pre-marketing evaluation. All reported events are included except those already

listed in Tables 1 & 2, those occurring in only one patient, event types that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/10 patients; infrequent adverse events are those occurring in less than 1/10 patients but at least 1/100 patients.

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

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

Gastrointestinal Disorders—Frequent: heartburn, abdominal cramp, indigestion. Infrequent: gastroesophageal reflux, bloating, abdominal distention, dyspepsia, increased stool frequency, belching, gas, chest pain, hemorroids, gagging, polyposis gastric, swallowing difficulty.

General—Frequent: allergy, pain in limb, fever, hot flashes, chest pain. Infrequent: edema of extremities, chills, lightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall.

Hemic and Lymphatic Disorders—Frequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical.

Metabolic and Nutritional Disorders—Frequent: increased weight, infrequent: decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia.

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

Psychiatric Disorders—Frequent: appetite increased, lethargy, irritability, concentration impaired. Infrequent: jitteriness, panic reaction, agitation, agitated, forgetfulness, depression aggravated, nervousness, restlessness, aggravated, suicide attempt, amnesia, anxiety attack, bruising, carboxy-drug craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, amnesia, social inhibition, auditory hallucination, marked decrease in libido. Reproductive Disorders/Female—Frequent: menstrual cramps, menstrual disorder. Infrequent: menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses.

Special Senses—Frequent: vision blurred, tinnitus. Infrequent: taste altered, nasal congestion, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste.

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

Events Reported Subsequent to the Marketing of Escitalopram
Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during postmarketing experience and were not observed during the pre-marketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, angioedema, atrial fibrillation, diplopia, dystonia, extrapyramidal signs, hypotension, hypokalemia, grand mal seizures (or convulsions), hepatitis, hypotension, myocardial infarction, neuroleptic malignant syndrome, orthostatic hypotension, paresthesias, pulmonary embolism, QT prolongation, rhabdomyolysis, serotonin syndrome, SIAH, thrombocytopenia, torsades de pointes, toxic epidermal necrolysis, ventricular tachycardia and ventricular tachycardias.

Events Reported Subsequent to the Marketing of Racemic Citalopram
Although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with racemic citalopram treatment and were not observed during the pre-marketing evaluation of citalopram: acute renal failure, akathisia, allergic reaction, anaphylaxis, anorexia, choreoathetosis, delirium, dyskinesia, eczema, erythema multiforme, gastrointestinal hemorrhage, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, myositis, neuroleptic malignant syndrome, nystagmus, pancreatitis, pruritus, proctodermatitis, profthirionitis, QT prolongation, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, torsades de pointes, toxic epidermal necrolysis and ventricular arrhythmia.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class
Lexapro is not a controlled substance.

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

OVERDOSE
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 antidepressants, overdoses of Lexapro in a patient who has taken an overdose of escitalopram have been rarely reported.

Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, include convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation).

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

DOSAGE AND ADMINISTRATION
Major Depressive Disorder
Initial Treatment

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

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

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

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

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

Maintenance Treatment
It is generally agreed that acute episodes of major depressive disorder may be treated with Lexapro for a period of 6 to 8 weeks. Systematic pharmacological therapy beyond response to the acute episode. Sustained evaluation of continuing Lexapro 10 or 20 mg for periods of up to 36 weeks in patients with major depressive disorder who responded while taking Lexapro during an 8-week, acute-treatment phase demonstrated a benefit of such maintenance treatment may be considered. Subsequently, the physician may consider continuing Lexapro. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Generalized Anxiety Disorder
Initial Treatment
The recommended starting dose of Lexapro is 10 mg once daily. If the dose is increased to 20 mg, this should occur after a minimum of one week. Lexapro should be administered once daily, in the morning or evening, with or without food.

Maintenance Treatment
Generalized anxiety disorder is recognized as a chronic condition. The physician should carefully consider the potential risks and benefits of treatment, 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.

Discontinuation of Treatment with Lexapro
Symptoms associated with discontinuation of Lexapro and other SSRIs 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 maintained dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Switching Patients to or from a Monoamine Oxidase Inhibitor
At least 14 days should elapse between discontinuation of an MAOI and initiation of Lexapro therapy. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI (see PRECAUTIONS and WARNINGS).

HOW SUPPLIED
5 mg Tablets:
NDC # 0456-2005-01
White to off-white, round, non-scored, film-coated, imprint "L" on one side of the tablet and "5" on the other side.
10 mg Tablets:
NDC # 0456-2010-01
NDC # 0456-2010-63
White to off-white, round, scored, film-coated, imprint on scored side with "L" on the left side and "10" on the right side.
Imprint on the non-scored side with "10".

20 mg Tablets:
NDC # 0456-2020-01
NDC # 0456-2020-63
White to off-white, round, scored, film-coated, imprint on scored side with "L" on the left side and "20" on the right side.
Imprint on the non-scored side with "20".

Oral Solution:
5 mg/5 mL peppermint flavor (240 mL) NDC # 0456-2011-08
Store at 25°C (77°F); excursions permitted to 15° - 30°C