

CENTER FOR DRUG EVALUATION AND RESEARCH

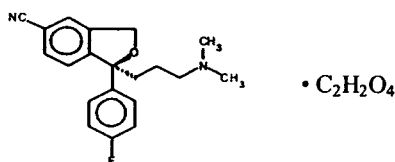
Application Number 21-440

FINAL PRINTED LABELING

LEXAPRO™
(escitalopram oxalate)

DESCRIPTION

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



The molecular formula is C₂₀H₂₁FN₂O • C₂H₂O₄ 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™ tablets are film coated, round tablets containing escitalopram oxalate in strengths equivalent to 5 mg, 10 mg or 20 mg escitalopram base. The 10 and 20 mg tablets are scored. The tablets also contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hydroxypropyl methyl cellulose, titanium dioxide, and polyethylene glycol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100 fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-

of escitalopram was shown in an 8-week fixed dose study that compared 10 mg/day Lexapro and 20 mg/day Lexapro to placebo and 40 mg/day citalopram, in outpatients between 18 and 65 years of age who met DSM-IV criteria for major depressive disorder. The 10 mg/day and 20 mg/day Lexapro treatment groups showed significantly greater mean improvement compared to placebo on the Montgomery Asberg Depression Rating Scale (MADRS). The 10 mg and 20 mg Lexapro™ groups were similar in mean improvement on the MADRS score.

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.

Longer-term efficacy of escitalopram in major depressive disorder has not been systematically evaluated; however, longer-term efficacy of racemic citalopram in this population has been established. In two longer-term studies, patients meeting DSM-III-R criteria for major depressive disorder who had responded (MADRS \leq 12) during an initial 6 or 8 weeks of acute treatment on racemic citalopram (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 racemic citalopram or to placebo, for up to 6 months of observation for relapse. In both studies, patients receiving continued racemic citalopram treatment experienced significantly lower relapse rates (MADRS \geq 22 in the fixed dose study; MADRS \geq 25 in the flexible dose study) 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 racemic citalopram.

In a third longer-term trial, patients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded (MADRS total score \leq 11) and continued to be improved (MADRS total score never exceeded 22 and returned to \leq 11 before randomization) during an initial 22-25 weeks of treatment on racemic citalopram (20-60 mg/day) were randomized to continuation of their same racemic citalopram dose or to placebo. The follow-up period to observe patients for relapse, defined either in terms of increases in the MADRS (MADRS total score $>$ 22) or a judgement by an independent review board that discontinuation was due to relapse, was for up to 72 weeks. Patients receiving continued racemic citalopram treatment experienced significantly lower relapse rates over the subsequent 72 weeks compared to those receiving placebo.

INDICATIONS AND USAGE

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 part, on the basis of extrapolation from the established effectiveness of racemic citalopram, of which escitalopram is the active isomer. In addition, the efficacy of escitalopram was shown in an 8-week controlled trial of outpatients whose diagnoses

corresponded most closely to the DSM-IV category of major depressive disorder (see Clinical Pharmacology).

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

The efficacy of Lexapro™ in hospitalized patients with major depressive disorders has not been adequately studied.

While the longer-term efficacy of Lexapro™ has not been systematically evaluated, the efficacy of racemic citalopram, of which escitalopram is the active isomer, in maintaining a response following 6 to 8 weeks of acute treatment in patients with major depressive disorder was demonstrated in two placebo-controlled trials, in which patients were observed for relapse for up to 24 weeks. The efficacy of racemic citalopram in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 22-25 weeks of treatment and were then followed for a period of up to 72 weeks was demonstrated in a third placebo-controlled trial (see 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.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOI's) is contraindicated (see Warnings).

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

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment

and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRI's and MAOI's suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro™ should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro™ before starting a MAOI.

PRECAUTIONS

General

Hyponatremia

One case of hyponatremia has been reported in association with Lexapro™ treatment. Several cases of hyponatremia or SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with racemic citalopram. All patients with these events have recovered with discontinuation of escitalopram or citalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder.

Activation of Mania/Hypomania

In placebo-controlled trials of Lexapro™, 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. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro™ should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro™ has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro™, no seizures occurred in subjects exposed to Lexapro™. Like other drugs effective in the treatment of major depressive disorder, Lexapro™ should be introduced with care in patients with a history of seizure disorder.

Suicide

The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. As with all drugs effective in the treatment of major depressive disorder, prescriptions for Lexapro™ should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Interference with Cognitive and Motor Performance

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

Use in Patients with Concomitant Illness

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

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

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

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

Information for Patients

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

In studies in normal volunteers, racemic citalopram in doses of 40 mg/day did not impair psychomotor performance. The effect of Lexapro™ on psychomotor coordination, judgment, or thinking has not been systematically examined in controlled studies.

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

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

Patients should be made aware that escitalopram is the active isomer of Celexa (citalopram hydrobromide) and that the two medications should not be taken concomitantly.

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

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

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

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

Laboratory Tests

There are no specific laboratory tests recommended.

Concomitant Administration with Racemic Citalopram

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

Drug Interactions

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

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

Monoamine Oxidase Inhibitors (MAOI's) - See Contraindications and Warnings.

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

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

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

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

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

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

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

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

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

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

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

Drugs Metabolized by Cytochrome P4502D6 - *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{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.

Metoprolol - Administration of 20 mg/day Lexapro™ for 21 days 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.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

When racemic citalopram was administered orally to male and female rats prior to and throughout mating and gestation at doses of 16/24 (males/females), 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.

Pregnancy

Pregnancy Category C

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

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

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

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

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 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.

Labor and Delivery

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

Nursing Mothers

Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breast feeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow up information was available. The decision whether to continue or discontinue either nursing or Lexapro™ therapy should take into account the risks of citalopram exposure for the infant and the benefits of Lexapro™ treatment for the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Approximately 6% of the 715 patients receiving escitalopram in controlled trials of Lexapro™ in major depressive disorder were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro™ between 10 and 20 mg. The number of

elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro™ cannot be ruled out.

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

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

ADVERSE REACTIONS

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

Among the 715 depressed patients who received Lexapro™ in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2 % of 592 patients receiving placebo. In two fixed dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro™ was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro™ was 10% which was significantly different from the rate of discontinuation for

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

Incidence of Adverse Events in Placebo-Controlled Clinical Trials

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 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 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*

<u>Body System / Adverse Event</u>	(Percentage of Patients Reporting Event)	
	<u>Lexapro™</u> (N=715)	<u>Placebo</u> (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%

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

¹Primarily ejaculatory delay.

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

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

Dose Dependency of Adverse Events

The potential dose dependency of common adverse events (defined as an incidence rate of $\geq 5\%$ in either the 10 mg or 20 mg LEXAPRO™ groups) was examined on the basis of the combined incidence of adverse events in two fixed dose trials. The overall incidence rates of adverse events in 10 mg LEXAPRO™ treated patients (66%) was similar to that of the placebo treated patients (61%), while the incidence rate in 20 mg/day LEXAPRO™ treated patients was greater (86%). Table 2 shows common adverse events that occurred in the 20 mg/day LEXAPRO™ group with an incidence that was approximately twice that of the 10 mg/day LEXAPRO™ group and approximately twice that of the placebo group.

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

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

Male and Female Sexual Dysfunction with SSRIs

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

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

of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

Table 3 shows the incidence rates of sexual side effects in patients with major depressive disorder in placebo controlled trials.

TABLE 3 Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials		
Adverse Event	LEXAPRO	Placebo
	In Males Only	
	(N=225)	(N=188)
Ejaculation Disorder (primarily ejaculatory delay)	9%	<1%
Decreased Libido	4%	2%
Impotence	3%	<1%
	In Females Only	
	(N=490)	(N=404)
Decreased Libido	2%	<1%
Anorgasmia	2%	<1%

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

Priapism has been reported with all SSRIs.

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

Vital Sign Changes

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

Weight Changes

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

Laboratory Changes

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

ECG Changes

Electrocardiograms from Lexapro™ (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for LEXAPRO™ and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for LEXAPRO™ and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither LEXAPRO™ nor racemic citalopram were associated with the development of clinically significant ECG abnormalities.

Other Events Observed During the Premarketing Evaluation of Lexapro™

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 999 patients treated with Lexapro™ for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Table 1, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro™, they were not necessarily caused by it.

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

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

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

Gastrointestinal Disorders - *Frequent*: vomiting, flatulence, heartburn, tooth ache, gastroenteritis, abdominal cramp, gastroesophageal reflux. *Infrequent*: bloating, increased stool frequency, abdominal discomfort, dyspepsia, belching, gagging, gastritis, hemorrhoids.

General - *Frequent*: allergy, pain in limb, hot flushes, fever, chest pain. *Infrequent*: edema of extremities, chills, malaise, syncope, tightness of chest, leg pain, edema, asthenia, anaphylaxis.

Hemic and Lymphatic Disorders - *Infrequent*: bruise, anemia, nosebleed, hematoma.

Metabolic and Nutritional Disorders - *Frequent*: increased weight, decreased weight. *Infrequent*: bilirubin increased, gout, hypercholesterolemia, hyperglycemia.

Musculoskeletal System Disorders - *Frequent*: arthralgia, neck/shoulder pain, muscle cramp, myalgia. *Infrequent*: jaw stiffness, muscle stiffness, arthritis, muscle weakness, arthropathy, back discomfort, joint stiffness, jaw pain.

Psychiatric Disorders - *Frequent*: dreaming abnormal, yawning, appetite increased, lethargy, irritability, concentration impaired. *Infrequent*: agitation, jitteriness, apathy, panic reaction, restlessness aggravated, nervousness, forgetfulness, suicide attempt, depression aggravated, feeling unreal, excitability, emotional lability, crying abnormal, depression, anxiety attack, depersonalization, suicidal tendency, bruxism, confusion, carbohydrate craving, amnesia, tremulousness nervous, auditory hallucination.

Reproductive Disorders/Female* - *Frequent*: menstrual cramps. *Infrequent*: menstrual disorder, menorrhagia, spotting between menses, pelvic inflammation.

*% based on female subjects only: N= 658

Respiratory System Disorders - *Frequent*: bronchitis, sinus congestion, coughing, sinus headache, nasal congestion. *Infrequent*: asthma, breath shortness, laryngitis, pneumonia, tracheitis.

Skin and Appendages Disorders - *Frequent*: rash. *Infrequent*: acne, pruritus, eczema, alopecia, dry skin, folliculitis, lipoma, furunculosis, dermatitis.

Special Senses - *Frequent*: vision blurred, ear ache, tinnitus. *Infrequent*: taste alteration, eye irritation, conjunctivitis, vision abnormal, visual disturbance, dry eyes, eye infection, pupils dilated.

Urinary System Disorders - *Frequent*: urinary tract infection, urinary frequency.
Infrequent: kidney stone, dysuria, urinary urgency.

Events Reported Subsequent to the Marketing of Racemic Citalopram

Although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment and were not observed during the premarketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Lexapro™ is not a controlled substance.

Physical and Psychological Dependence

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

OVERDOSAGE

Human Experience

There have been three reports of Lexapro™ overdose involving doses of up to 600 mg. All three patients recovered and no symptoms associated with the overdoses were reported. In clinical trials of racemic citalopram, there were no reports of fatal citalopram overdose involving overdoses of up to 2000 mg. During the postmarketing evaluation of

citalopram, like other SSRIs, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely reported.

Postmarketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920 mg and 2800 mg), as well as non-fatal overdoses of up to 6000 mg. Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, sinus tachycardia, and convulsions. In more rare cases, observed symptoms included amnesia, confusion, coma, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of Torsades de pointes).

Management of Overdose

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

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

DOSAGE AND ADMINISTRATION

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.

Maintenance Treatment

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Lexapro™ has not been evaluated in controlled, longer-term trials. However, systematic evaluation of racemic citalopram in two studies has demonstrated a benefit of maintaining treatment following response occurring during 6 to 8 weeks of initial treatment. In both studies, patients were observed for relapse during an observation period of up to 24 weeks. In one study, patients were assigned randomly to placebo or to the same dose of racemic citalopram (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 racemic citalopram 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. A third longer-term study has demonstrated the efficacy of racemic citalopram in maintaining an antidepressant response in patients with recurrent depression who had responded and continued to be improved during an initial 22-25 weeks of treatment and were then observed for relapse for a period of up to 72 weeks (see Clinical Efficacy Trials under Clinical Pharmacology). Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of Lexapro™ therapy. Similarly, at least 14 days should be allowed after stopping Lexapro™ before starting a MAOI (see Contraindications and Warnings).

HOW SUPPLIED

5 mg Tablets:

Bottle of 30	NDC # 0456-2005-30
Bottle of 100	NDC # 0456-2005-01
Bottle of 1000	NDC # 0456-2005-00
10 x 10 Unit Dose	NDC # 0456-2005-63

White to off-white, round, non-scored film coated. Imprint "FL" on one side of the tablet and "5" on the other side.

10 mg Tablets:

Bottle of 30	NDC # 0456-2010-30
Bottle of 100	NDC # 0456-2010-01
Bottle of 1000	NDC # 0456-2010-00

10 x 10 Unit Dose NDC # 0456-2010-63

White to off-white, round, scored film coated. Imprint on scored side with "F" on the left side and "L" on the right side.
Imprint on the non-scored side with "10"

20 mg Tablets:

Bottle of 30	NDC # 0456-2020-30
Bottle of 100	NDC # 0456-2020-01
Bottle of 1000	NDC # 0456-2020-00
10 x 10 Unit Dose	NDC # 0456-2020-63

White to off-white, round, scored film coated. Imprint on scored side with "F" on the left side and "L" on the right side.
Imprint on the non-scored side with "20".

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

ANIMAL TOXICOLOGY

Retinal Changes in Rats

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

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

Cardiovascular Changes in Dogs

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

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Attachment

Approved Labeling

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

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LEXAPRO NDA 21-323 AP LABELING 04

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