A Complimentary Relationship: Psychotherapy and Medication for Anxiety and Depressive Disorders

By Jack M. Gorman, MD

When an internist diagnoses type 2 diabetes mellitus or essential hypertension in a patient, it is very likely that the initial recommendation for therapy will not include a prescription for medication. Unless the situation is severe or emergent, the physician is most likely to recommend a regimen of diet, exercise, and stress management and ask the patient to return for a reevaluation in several weeks. Only if the attempt at behavioral change is not successful will medication likely become part of the regimen. Even so, the attempt at lifestyle management will be reinforced as part of the ongoing management of the illness.

This does not mean that physicians believe that diabetes and hypertension are purely "psychological" issues. Rather, they understand that emotion and behavior have a profound impacts on somatic function, that the sensitivity of cells to insulin or the caliber of blood vessels is determined by many factors, some of which are controlled by the central nervous system.

It is ironic, then, that many psychiatrists seem to lost faith in these essential truths. Not that long ago, psychotherapy reigned as the champion of first-line interventions in psychiatry and medications were looked upon with suspicion. Today, of course, we know that psychiatric medications are safe and effective, often necessary to manage serious illnesses, and sometimes life-saving. Somehow, however, the fact that psychotherapies are also safe and effective and sometimes superior to medication management is insufficiently acknowledged.

Nowhere is this more evident than in the treatment of anxiety disorders. I am constantly asked to lecture on the treatment of anxiety and depression, but the expectation is always that I will review what is known about the pharmacologic management of these common conditions and perhaps give clinicians and patients hope by describing what is in the pipeline of the pharmaceutical companies. I am always glad to do this, because the pharmacologic management of anxiety disorders iseffective and there are fascinating molecules now in development that promise even better outcomes.

I am also astonished to realize that psychiatrists do not have the same enthusiasm to learn about psychosocial interventions. The simple fact is that for every anxiety disorder—and for depression as well—there is now empirical evidence that at least one form of psychotherapy is at least as effective for most cases as medication. Furthermore, psychotherapy research has consistently shown that in some situations psychotherapy is more durable than medication management, leading to longer duration of symptom-free status.

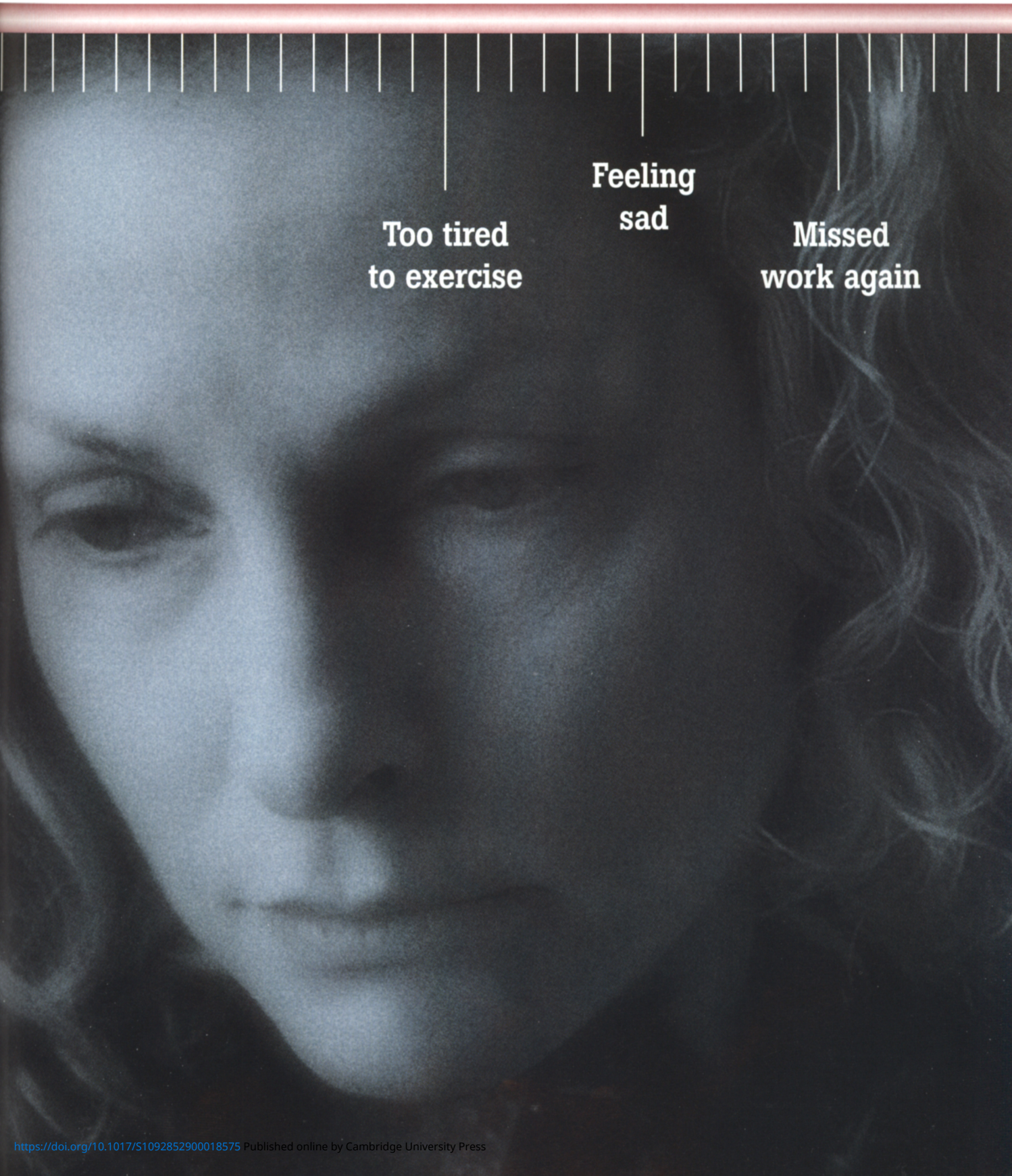
We are delighted that Edna Foa, PhD, and Martin Franklin, PhD, along with their colleagues at the University of Pennsylvania in Philadelphia, have collected the data that make the aforementioned assertions undeniable. It is my opinion that every patient with an anxiety disorder should be told that both cognitive-behavioral psychotherapy and medication have been proven to work in rigorously controlled research studies; that there is no evidence upon which to decide which is better; that cognitive-behavioral psychotherapy has fewer adverse side effects; and that after treatment completion patient treated with psychotherapy tend to stay well longer than those who have been treated with medication. The patient should be given a choice of which modality to accept, or to have both. One model that our group and others is currently studying is to offer cognitive-behavioral therapy to all patients first, reserving medication for those who do not derive adequate benefit. It seems that we may have learned something about psychotherapy and behavior from our internal medicine colleagues.

I would also like to mention that *CNS Spectrums* is now receiving many very good, unsolicited research and review articles from authors around the world. This is a welcome development we wish to encourage. We are particularly interested in receiving articles from both psychiatrists and neurologists and we will work with authors for whom English is not their first language. In this way, we hope to continue to be the forum in which both disciplines learn about the best in each other's work and that brings to our attention the fine work being done all around the world.

We want to take this opportunity to alert our readers to a new feature in *CNS Spectrums*—letters to the editor will now be accepted. All letters will be peer-reviewed and edited, so that acceptance of a letter is not guaranteed, but we very much want to hear from you and will make every effort to publish as many letters as possible. We will entertain letters that comment on articles already published in *CNS Spectrums*, interesting case reports, and new ideas. In all cases, letters should not exceed 500 words in length and should not include figures or tables. CNS

Dr. Gorman is the editor of CNS Spectrums *and Leiber professor of psychiatry at Mount Sinai School of Medicine in New York City.*

How to measure your patients' depression



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*Full antidepressant effect may take 4 to 6 weeks.

LEXAPRO is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients with a hypersensitivity to escitalopram oxalate or any of the ingredients in LEXAPRO. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with LEXAPRO.

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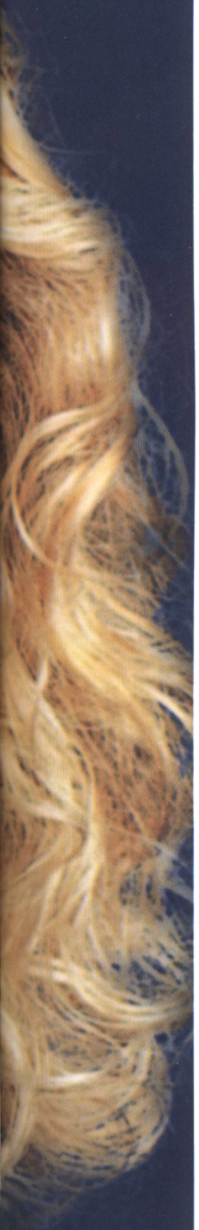

How to measure Well-tolerated therapy in a powerful SSRI

LEXAPRO 10 mg/day demonstrated comparable efficacy to CELEXA 40 mg/day[1]

Significantly improved depression for many patients beginning at week 1 or 2*[1]

Effectively treats anxiety symptoms associated with depression[1]

Introducing the isomer of CELEXA™ (citalopram HBr)

NEW

Lexapro™

escitalopram oxalate

Well-tolerated strength

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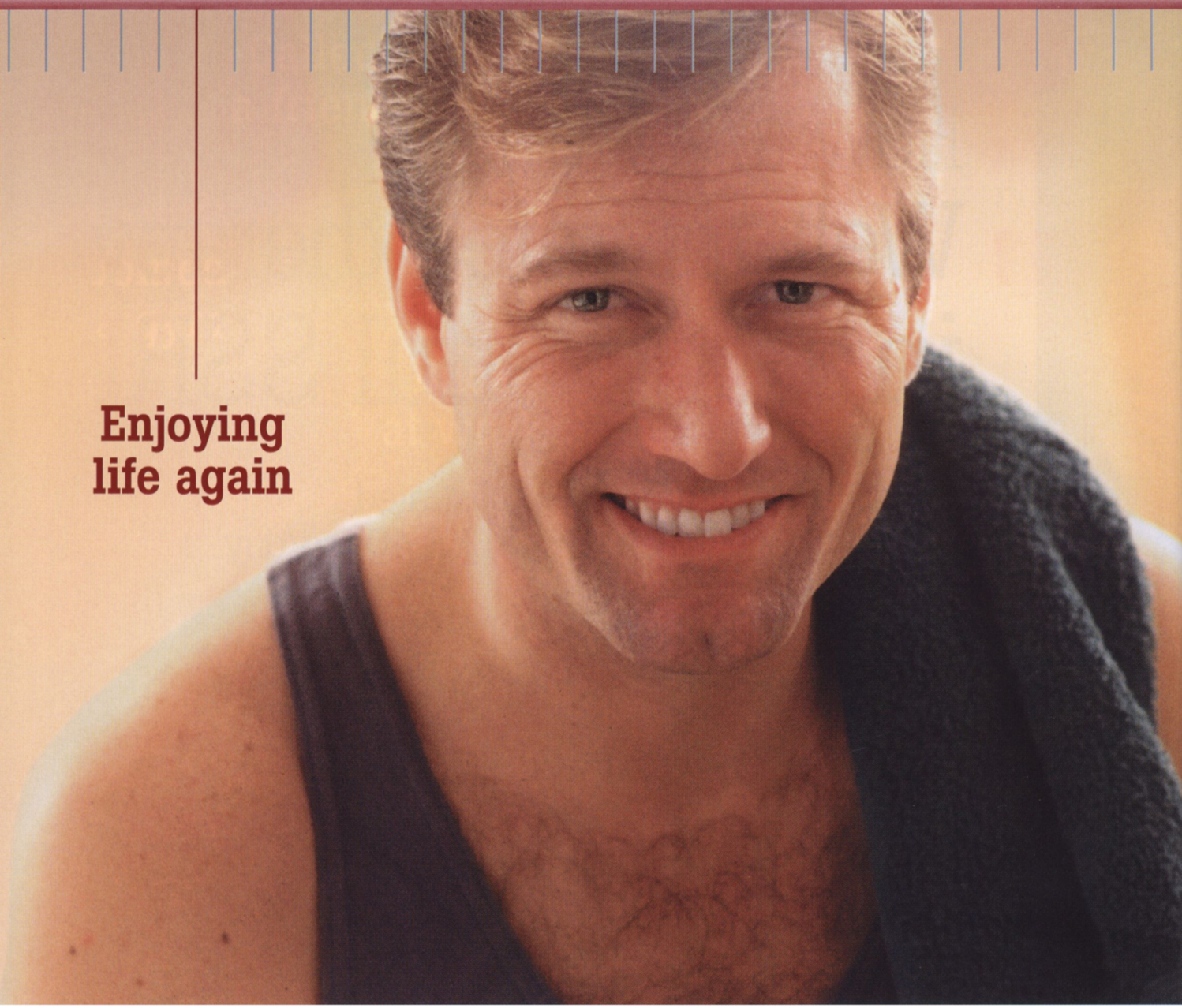
How to measure Powerful SSRI therapy



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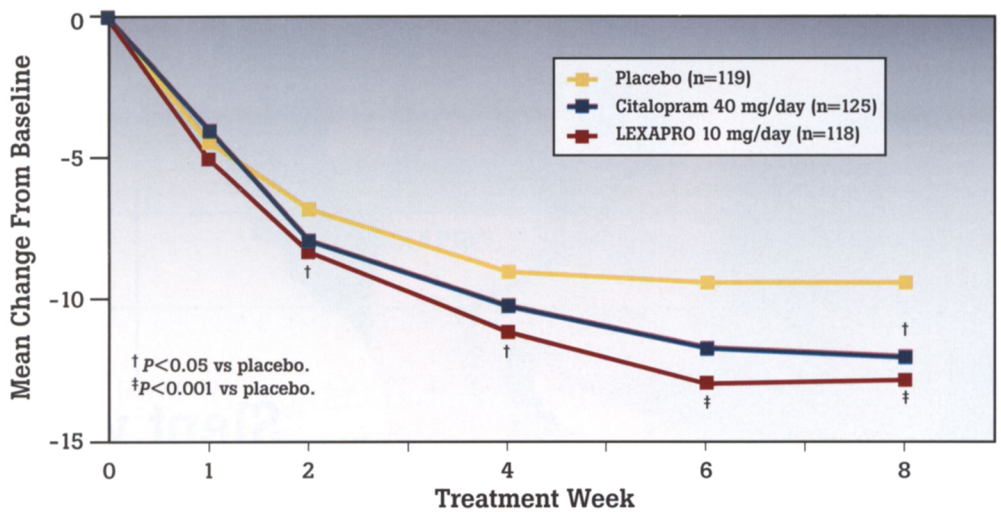
In the treatment of major depression

LEXAPRO 10 mg/day significantly improved depression*[1,2]

MADRS Total Score by Visit



Study design: 8-week, randomized, double-blind, placebo-controlled, fixed-dose (LEXAPRO 10 or 20 mg/day; citalopram 40 mg/day), U.S. multicenter trial in adult patients with DSM-IV diagnosed major depression (MADRS ≥22, lasting ≥4 weeks). Overall mean MADRS=28.9 at baseline.[1]

LEXAPRO 10 mg/day demonstrated comparable efficacy to CELEXA™ (citalopram HBr) 40 mg/day[1]

Lexapro™
escitalopram oxalate
Well-tolerated strength

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How to measure
Well-tolerated therapy

The most common adverse events reported with LEXAPRO vs placebo (approximately 5% or greater and approximately 2X placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, and fatigue.

Please see brief summaries of prescribing information for LEXAPRO and CELEXA™ (citalopram HBr) at end of advertisement.

References: 1. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry*. 2002;63:331-336.
2. Data on file, Forest Laboratories, Inc. **3.** LEXAPRO [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc: 2002.

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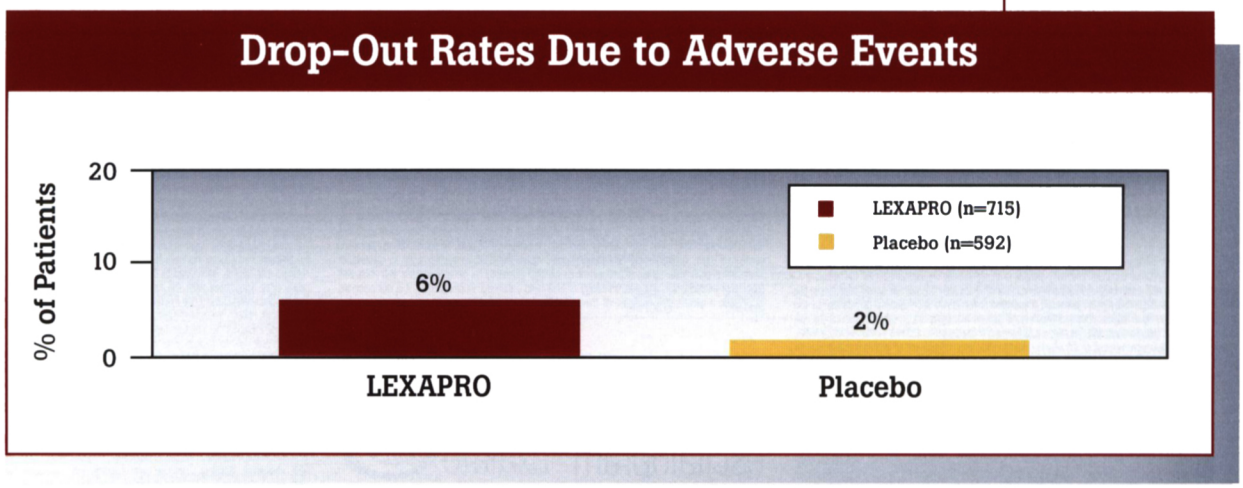
In the comprehensive safety database*

Low drop-out rates due to adverse events[3]



- LEXAPRO 10 mg/day had drop-out rates due to adverse events comparable to placebo[3]

Favorable side-effect profile

- Only one adverse event occurred at a rate above 10%[3]
- LEXAPRO patients experienced no clinically important change in body weight[3]

Simple 10 mg/day starting dose for all patients[3]

- 10 mg/day starting and maintenance dose for most patients

*Includes patients treated with 10 to 20 mg/day.

Lexapro™
escitalopram oxalate
Well-tolerated strength

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LEXAPRO™
(escitalopram oxalate) TABLETS

Brief Summary: For complete details, please see full prescribing information for LEXAPRO™

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). **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. **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/m²] 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/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 (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/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 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*
(Percentage of Patients Reporting Event)

Body System / Adverse Event	LEXAPRO™ (N=715)	Placebo (N=592)
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder †	9%	<1%
Impotence‡	3%	<1%
Anorgasmia§	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 ≥ LEXAPRO™: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. Primarily ejaculatory delay. †Denominator used was for males only (N=225 LEXAPRO™; N=188 placebo). ‡Denominator 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 ≥ 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%). **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 2 shows the incidence rates of sexual side effects in patients with major depressive disorder in placebo controlled trials.

TABLE 2
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. **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).

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08/02

Celexa
citalopram HBr

Tablets/Oral Solution

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Brief Summary: For complete details, please see full prescribing information for Celexa. **INDICATIONS AND USAGE** Celexa (citalopram HBr) is indicated for the treatment of depression. The efficacy of Celexa in the treatment of depression was established in 4-6 week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation. The antidepressant action of Celexa in hospitalized depressed patients has not been adequately studied. The efficacy of Celexa in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials. Nevertheless, the physician who elects to use Celexa for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. **CONTRAINDICATIONS** Concomitant use in patients taking monoamine oxidase inhibitors (MAOI's) is contraindicated (see WARNINGS). Celexa is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in Celexa. **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 an 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 Celexa should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Celexa before starting an MAOI. PRECAUTIONS General** Hyponatremia Several cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Celexa treatment. All patients with these events have recovered with discontinuation of Celexa and/or medical intervention. Activation of Mania/ Hypomania In placebo-controlled trials of Celexa,some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with Celexa and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants. As with all antidepressants, Celexa should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of citalopram have been observed in animal studies, Celexa has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Celexa, seizures occurred in 0.3% of patients treated with Celexa (a rate of one patient per 98 years of exposure) and 0.5% of patients treated with placebo (a rate of one patient per 50 years of exposure). Like other antidepressants, Celexa should be introduced with care in patients with a history of seizure disorder. Suicide The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Celexa should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Interference With Cognitive and Motor Performance In studies in normal volunteers, Celexa in doses of 40 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgement, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities. Use in Patients With Concomitant Illness Clinical experience with Celexa in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Celexa in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Celexa has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's pre-marketing testing. However, the electrocardiograms of 1116 patients who received Celexa in clinical trials were evaluated, and the data indicate that Celexa is not associated with the development of clinically significant ECG abnormalities. In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Celexa in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended. Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Celexa, however, it should be used with caution in such patients. **Drug Interactions** CNS Drugs – Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol – Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking Celexa is not recommended. Monoamine Oxidase Inhibitors (MAOI's) – See CONTRAINDICATIONS and WARNINGS. Cimetidine – In subjects who had received 21 days of 40 mg/day Celexa, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin – In subjects who had received 21 days of 40 mg/day Celexa, combined administration of Celexa and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium – Coadministration of Celexa (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalopram, caution should be exercised when Celexa and lithium are coadministered. Theophylline – Combined administration of Celexa (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. Sumatriptan – There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (eg, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised. Warfarin – Administration of 40 mg/day Celexa for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine – Combined administration of Celexa (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered. Triazolam – Combined administration of Celexa (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. Ketoconazole – Combined administration of Celexa (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. CYP3A4 and CYP2C19 Inhibitors – *In vitro* studies indicated that CYP3A4 and CYP2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Metoprolol – Administration of 40 mg/day Celexa for 22 days resulted in a two-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Celexa and metoprolol had no clinically significant effects on blood pressure or heart rate. Imipramine and Other Tricyclic Antidepressants (TCAs) – *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of Celexa (40 mg/day for 10 days) with the tricyclic antidepressant imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown.

Nevertheless, caution is indicated in the coadministration of TCA's with Celexa. Electroconvulsive Therapy (ECT) – There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and Celexa. **Pregnancy** Pregnancy Category C – There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of Celexa on labor and delivery in humans is unknown. **Nursing Mothers** As has been found to occur with many other drugs, citalopram is excreted in human breast milk. The decision whether to continue or discontinue either nursing or Celexa therapy should take into account the risks of citalopram exposure for the infant and the benefits of Celexa treatment for the mother. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** Of 4422 patients in clinical studies of Celexa,1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with Celexa in clinical trials received daily doses between 20 and 40 mg. In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively. 20 mg/day is the recommended dose for most elderly patients. **ADVERSE REACTIONS** The premarketing development program for Celexa included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Celexa varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Findings Observed in Short-Term, Placebo-Controlled Trials** Adverse Events Associated With Discontinuation of Treatment Among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (ie, associated with discontinuation in at least 1% of Celexa-treated patients and at a rate at least twice that of placebo) are shown in **TABLE 1**. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in this table.

TABLE 1.
Adverse Events Associated With Discontinuation of Treatment in Short-Term, Placebo-Controlled Depression Trials

	Percentage of Patients Discontinuing Due to Adverse Event	
Body System/Adverse Event	**Celexa (N=1063)**	**Placebo (N=446)**
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomiting	1%	0%
Central and Peripheral Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Adverse Events Occurring at an Incidence of 2% or More Among Celexa-Treated Patients **TABLE 2** enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with Celexa and for which the incidence in patients treated with Celexa was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The only commonly observed adverse event that occurred in Celexa patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see **TABLE 2**).

TABLE 2.
Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Celexa (N=1063)**	**Placebo (N=446)**
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central & Peripheral Nervous System Disorders		
Tremor	8%	6%
Gastrointestinal Disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%
Vomiting	4%	3%
Abdominal Pain	3%	2%
General		
Fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea[1]	3%	2%
Libido Decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation Disorder[2,3]	6%	1%
Impotence[3]	3%	<1%

* Events reported by at least 2% of patients treated with Celexa are reported, except for the following events which had an incidence in placebo ≥Celexa: headache, asthenia, dizziness,

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constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain. [1] Denominator used was for females only (N=638 Celexa; N=252 placebo). [2] Primarily ejaculatory delay. [3] Denominator used was for males only (N=425 Celexa; N=194 placebo). Dose Dependency of Adverse Events The potential relationship between the dose of Celexa administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or Celexa 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response ($p<.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning. Male and Female Sexual Dysfunction With SSRI's 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 re-uptake 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. The table below displays the incidence of sexual side effects reported by at least 2% of patients taking Celexa in a pool of placebo-controlled clinical trials in patients with depression.

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

In female depressed patients receiving Celexa, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively. There are no adequately designed studies examining sexual dysfunction with citalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRI's, physicians should routinely inquire about such possible side effects. Vital Sign Changes Celexa and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Celexa treatment. In addition, a comparison of supine and standing vital sign measures for Celexa and placebo treatments indicated that Celexa treatment is not associated with orthostatic changes. Weight Changes Patients treated with Celexa in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients. Laboratory Changes Celexa and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Celexa treatment. ECG Changes Electrocardiograms from Celexa (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals. **Other Events Observed During the Premarketing Evaluation of Celexa (citalopram HBr)** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by patients treated with Celexa at multiple doses in a range of 10 to 80 mg/day during any phase of a trial within the premarketing database of 4422 patients. All reported events are included except those already listed in **TABLE 2** or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasize that although the events reported occurred during treatment with Celexa, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Cardiovascular – *Frequent:* tachycardia, postural hypotension, hypotension. *Infrequent:* hypertension, bradycardia, edema (extremities), angina pectoris, extrasystoles, cardiac failure, flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. *Rare:* transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block. Central and Peripheral Nervous System Disorders – *Frequent:* paresthesia, migraine. *Infrequent:* hyperkinesia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. *Rare:* abnormal coordination, hyperesthesia, ptosis, stupor. Endocrine Disorders – *Rare:* hypothyroidism, goiter, gynecomastia. Gastrointestinal Disorders – *Frequent:* saliva increased, flatulence. *Infrequent:* gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. *Rare:* colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups. General – *Infrequent:* hot flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms. *Rare:* hayfever. Hemic and Lymphatic Disorders – *Infrequent:* purpura, anemia. epistaxis, leukocytosis, leucopenia, lymphadenopathy. *Rare:* pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding. Metabolic and Nutritional Disorders – *Frequent:* decreased weight, increased weight. *Infrequent:* increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. *Rare:* billirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration. Musculoskeletal System Disorders – *Infrequent:* arthritis, muscle weakness, skeletal pain. *Rare:* bursitis, osteoporosis. Psychiatric Disorders – *Frequent:* impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. *Infrequent:* increased libido, aggressive reaction, paronina, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. *Rare:* catatonic reaction, melancholia. Reproductive Disorders/Female* – *Frequent:* amenorrhea. *Infrequent:* galactorrhea, breast pain, breast enlargement, vaginal hemorrhage. *% based on female subjects only: 2955 Respiratory System Disorders – *Frequent:* coughing. *Infrequent:* bronchitis, dyspnea, pneumonia. *Rare:* asthma, laryngitis, bronchospasm, pneumonitis, sputum increased. Skin and Appendages Disorders – *Frequent:* rash, pruritus. *Infrequent:* photosensitivity reaction, urticaria, acne, skin discoloration, eczema. alopecia, dermatitis, skin dry, psoriasis. *Rare:* hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani. Special Senses – *Frequent:* accommodation abnormal, taste perversion. *Infrequent:* tinnitus, conjunctivitis, eye pain. *Rare:* mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss. Urinary System Disorders – *Frequent:* polyuna. *Infrequent:* micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare:* facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain. **Other Events Observed During the Non-US Postmarketing Evaluation of Celexa (citalopram HBr)** It is estimated that over 30 million patients have been treated with Celexa since market introduction. Although no causal relationship to Celexa treatment has been found, the following adverse events have been reported to be temporally associated with Celexa treatment, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancrealitis, priapism, prolactinemia. prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion,thrombocytopenia, thrombosis, ventricular arrhythmia, Torsades de pointes, and withdrawal syndrome. **OVERDOSAGE Human Experience** Although there were no reports of fatal citalopram overdose in clinical trials involving overdoses of up to 2000 mg, 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 nonfatal 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, and sinus tachycardia. In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of Torsades de pointes).

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

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