DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Amy J. Rubin
Director, Regulatory Affairs
Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

RE: NDAs 20-822 and 21-046
Celexa (citalopram HBr)
MACMIS #10853

Dear Ms. Rubin:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified a promotional visual aid (40-221527) and brochure (40-221526) for Celexa (citalopram HBr) that are misleading, lacking fair balance, or otherwise in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations.

Specifically, DDMAC objects to the following:

1. Because an active control study of depression without a placebo is uninformative (i.e., there is no way to know whether the trial had assay sensitivity and could have distinguished treatments that differ from one another), such a study cannot be used to support a statement of similar or equivalent effectiveness. Comparative claims for Celexa that are based on clinical trials that do not use a placebo control are therefore misleading because they are not adequately substantiated. Examples of misleading comparative claims include:

   "Celexa and paroxetine both produced clinically significant reductions in major depression at similar doses"

   "Celexa 20-40 mg/day and paroxetine 20-40 mg/day effectively treated major depression"

   "Celexa and paroxetine both produced clinically significant reductions in anxiety symptoms at similar doses"

   "Celexa and paroxetine both significantly reduced anxiety symptoms associated with depression"

These misleading claims (e.g., pages 6 and 7 in brochure 40-221526; pages 3 and 10 in visual aid 40-221527) are based on a 24-week flexible dose study with no placebo control.

2. In addition, the promotional materials cited above include presentations of gastrointestinal adverse events that are misleading because they minimize one of the most important set of adverse events of Celexa (i.e., the gastrointestinal adverse effects). Specifically, these presentations (e.g., tables on page 3 of brochure 40-221526 and page 4 of the visual aid 40-221527) are based on a small clinical study that was not adequately designed to support safety claims. Further, these presentations are not consistent with the approved product labeling.

To address these objections, DDMAC recommends that Forest do the following:

1. Immediately discontinue the use of these and any other promotional materials with the same or similar issues.

2. Respond to this letter within ten days. Your response should include a statement of your intent to comply with the above, a list of all promotional materials with the same or similar issues, and your methods for discontinuing these promotional materials.

If you have questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID# 10853 in addition to the NDA numbers.

Sincerely,

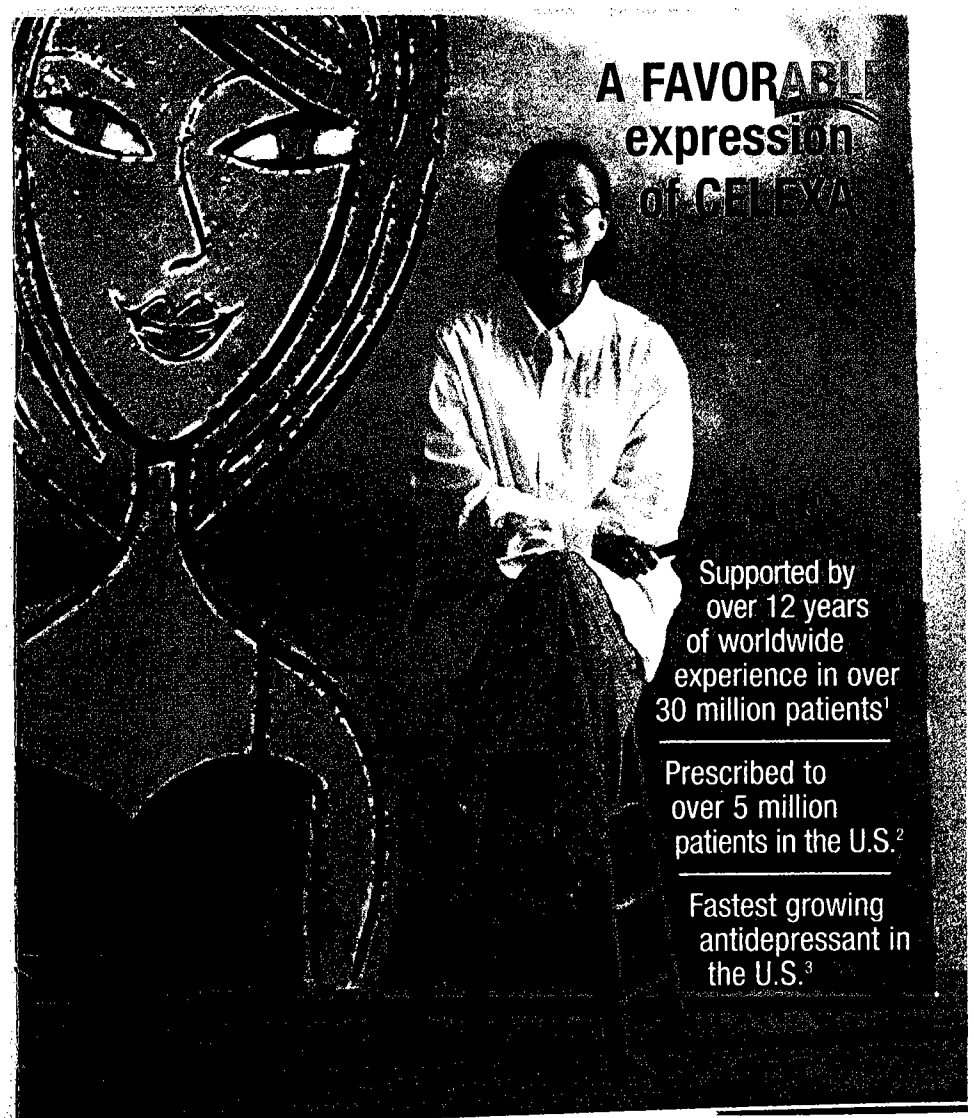
{See appended electronic signature page}

Lisa L. Stockbridge, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Lisa Stockbridge
9/13/02 12:13:10 PM



Celexa™
citalopram HBr

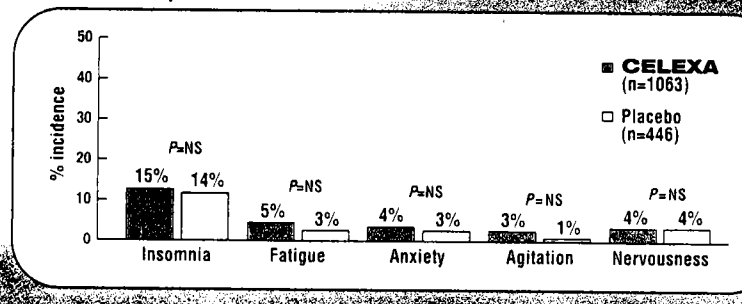
FOR DEPRESSION

Celexa

Favorable side-effect profile in short-term treatment

*In short-term clinical trials**

No statistically significant insomnia, fatigue, anxiety, agitation, or nervousness vs placebo[1]



GI side effects vs placebo[1]

CELEXA (n=1063)	9%	8%	5%	21%	4%
Placebo (n=446)	9%	5%	4%	14%	3%

*Pooled data from placebo-controlled depression trials for 4 to 6 weeks in duration.

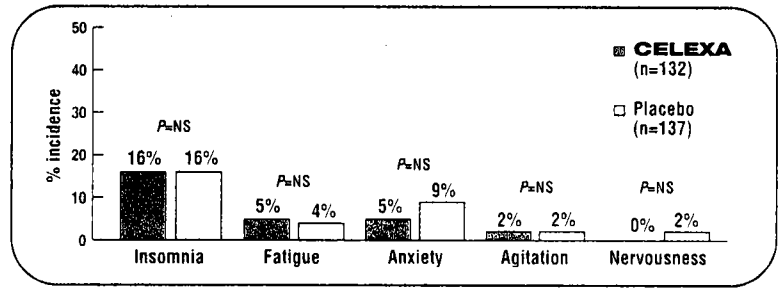
- Nausea generally resolves over time
- The most frequent adverse events reported with CELEXA vs placebo in clinical trials were nausea (21% vs 14%), dry mouth (9% vs 7%), somnolence (8% vs 5%), and ejaculation disorder (5% vs 1%)

Celexa

Favorable side-effect profile in long-term treatment

*In a long-term clinical trial**

No statistically significant insomnia, fatigue, anxiety, agitation, or nervousness vs placebo[1]



GI side effects vs placebo[1]

CELEXA (n=132)	2%	4%	2%	6%	5%
Placebo (n=137)	2%	2%	3%	10%	3%

*Study design: Safety data were taken from the final phase of a 6- to 24-month, double-blind, placebo-controlled study in patients with a history of at least 2 prior depressive episodes. 269 patients who responded (MADRS <12 from a baseline MADRS ≥22) during 25 weeks of acute open-label treatment with CELEXA (flexibly dosed, 20-60 mg/day) were randomized to either their established effective dose of CELEXA or placebo.[1]

Celexa
citalopram HBr™

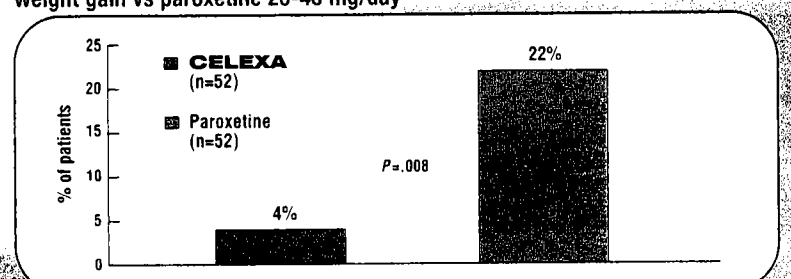
Well-tolerated SSRI therapy

Celexa

Low incidence of weight gain in long-term treatment

In a 6-month trial

Significantly fewer patients treated with CELEXA 20-40 mg/day experienced weight gain vs paroxetine 20-40 mg/day[5]



Study design: 6-month, double-blind, randomized, parallel, flexible-dose (CELEXA 20-40 mg/day; paroxetine 20-40 mg/day); U.S. multicenter trial; n=104 patients with anxious depression. Mean daily dose for CELEXA was 27.4 mg/day and for paroxetine, 28.6 mg/day. Significant weight gain is defined as ≥7% increase in weight.

- Only 4% of CELEXA-treated patients experienced significant weight gain vs 22% of patients treated with paroxetine[5]

Source: Jefferson JW, Greist JH. Presented at the 39th Annual Meeting, American College of Neuropsychopharmacology, Dec 2000.

In a separate study

CELEXA was not associated with clinically significant long-term weight changes[4]

- CELEXA therapy was associated with a mean weight increase of only 1.5 kg after 12 months[4]

The most frequent adverse events reported with CELEXA vs placebo (combined data [illegible]

Celexa

Does not interfere with the metabolism of many drugs*[1,6]

P450 isozyme inhibition by SSRIs *in vitro*[6]

	Human				
	3A4	2D6	2C9	2C19	1A2
CELEXA	0	+	+	0	0
Fluoxetine	++	+++	+	++	++
Paroxetine	+	+++	+	+	+
Sertraline	+	+	+	++	+

0 = minimal or zero inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = strong inhibition.

Source: Greenblatt DJ, et al. *J Clin Psychiatry.* 1998;59(suppl 15):19-27.

- CELEXA does not inhibit CYP3A4 and CYP2C9 *in vitro*[6]
- CELEXA is a weak inhibitor of CYP2D6, CYP1A2, and CYP2C19[6]

The clinical significance of *in vitro* data is unknown.

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

†*In vitro* enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, and CELEXA would be expected to have little inhibitory effect on *in vivo* metabolism by this enzyme. *In vivo* data demonstrating a lack of this effect are limited to carbamazepine and warfarin.

No dosage adjustment recommended with:

- Digoxin
- Warfarin
- Cimetidine
- Carbamazepine
- Theophylline†

May be used with highly protein-bound drugs

- Low plasma protein binding (approximately 80%) *in vitro*

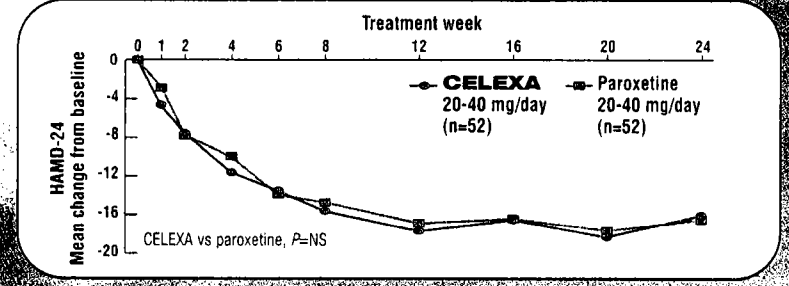
Celexa
citalopram HBr™

Well-tolerated SSRI therapy

Celexa

Effectively treats major depression

In a 6-month clinical trial
CELEXA 20-40 mg/day and paroxetine 20-40 mg/day effectively treated major depression[5]



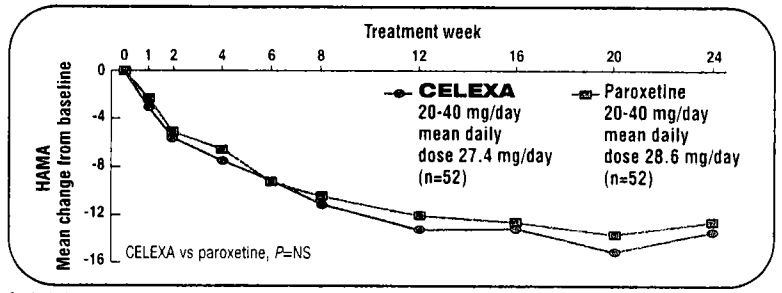
Study design: 24-week, double-blind, randomized, parallel, flexible-dose study (CELEXA 20-40 mg/day; paroxetine 20-40 mg/day) U.S. multicenter trial in 104 patients with depression and associated anxiety (HAMD-24 ≥18 and HAMA ≥17 at baseline). Baseline HAMD-24 mean total score: CELEXA, 25.94; paroxetine, 25.67. Mean daily dose for CELEXA was 27.4 mg/day and for paroxetine 28.6 mg/day.

- CELEXA and paroxetine both produced clinically significant reductions in major depression at similar doses (mean daily dose 27.4 mg/day and 28.6 mg/day, respectively)[5]

Celexa

CELEXA and paroxetine both significantly reduced anxiety symptons associated with depression[5]

Clinical trial of CELEXA 20-40 mg/day and paroxetine 20-40 mg/day[5]



Study design: 24-week, double-blind, randomized, parallel, flexible-dose study (CELEXA 20-40 mg/day; paroxetine 20-40 mg/day) U.S. multicenter trial in 104 patients with depression and associated anxiety (HAMD-24 ≥18 and HAMA ≥17 at baseline). Baseline HAMA mean total score: CELEXA, 23.02; paroxetine, 22.20. Mean daily dose for CELEXA was 27.4 mg/day and for paroxetine 28.6 mg/day.

- CELEXA and paroxetine both produced clinically significant reductions in anxiety symptoms at similar doses (mean daily dose 27.4 mg/day and 28.6 mg/day, respectively)[5]

Source: Jefferson JW, Greist JH. Presented at the 39th Annual Meeting, American College of Neuropsychopharmacology, Dec 2000.

Celexa
citalopram HBr™
Well-tolerated SSRI therapy

Celexa

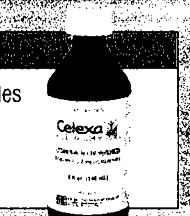
Convenient QD dosing

Once-daily 20 mg starting dose for all patients[7]

- Initial dose of 20 mg once daily, generally with an increase to 40 mg once daily
- Doses of more than 40 mg are not ordinarily necessary
- Dose increases should occur in 20 mg increments at intervals of no less than 1 week
- May be taken any time of day with or without food
- Available in 10 mg tablets for more flexible dosing

CELEXA is available in two forms

Tablets	Oral solution
10 mg	8-ounce (240 mL) bottles
20 mg	1 tsp contains 10 mg
	— sugar free
40 mg	— alcohol free



20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients

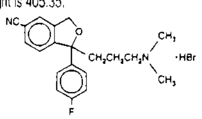
References: 1. Data on file, Forest Laboratories, Inc. **2.** Prescription Audit, 2000, NDC Health Information Services. **3.** IMS National Prescription Audit, 2001. **4.** Kocsis J. Effects on body weight of the SSRI citalopram. Presented at the 37th Annual Meeting, American College of Neuropsychopharmacology, 1998; New York, NY. **5.** Jefferson JW, Greist JH. A double-blind comparison of citalopram and paroxetine in the treatment of patients with depression and anxiety. Presented at the 39th Annual Meeting, American College of Neuropsychopharmacology, 2000; San Juan, Puerto Rico. **6.** [illegible]

Celexa™
citalopram HBr

DESCRIPTION

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

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



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

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

Celexa 10 mg tablets are film coated, oval tablets containing citalopram HBr in strengths equivalent to 10 mg citalopram base. Celexa 20 mg and 40 mg tablets are film coated, oval, scored tablets containing citalopram HBr in strengths equivalent to 20 mg or 40 mg citalopram base. The tablets also contain the following inactive ingredients: Copolyvidone, Corn Starch, Crosscarmellose Sodium, Glycerin, Lactose Monohydrate, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Microcrystalline Cellulose, Polyethylene Glycol, and Titanium Dioxide. Iron Oxides are used as coloring agents in the beige (10 mg) and pink (20 mg) tablets.

Celexa oral solution contains citalopram HBr equivalent to 2mg/mL citalopram base. It also contains the following inactive ingredients: Sorbitol, Purified Water, Propylene Glycol, Methylparaben, Natural Peppermint Flavor, and Propylparaben.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

Citalopram has no or very low affinity for $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, dopamine D_1 and D_2, α_1-, α_2-, and β-adrenergic, histamine H_1, gamma aminobutyric acid (GABA), muscarinic, cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular effects of other psychotropic drugs.

Pharmacokinetics

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

Absorption and Distribution

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

Metabolism and Elimination

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

Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide and a deaminated propionic acid derivative. In humans, unchanged citalopram is the predominant compound in plasma. At steady state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram

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

Population Subgroups

Age–Citalopram pharmacokinetics in subjects ≥60 years of age were compared to younger subjects in two normal volunteer studies. In a single dose study, citalopram AUC and half-life were increased in the elderly subjects by 30% and 50%, respectively, whereas in a multiple dose study they were increased by 23% and 30%, respectively. 20 mg is the recommended dose for most elderly patients (see Dosage and Administration).

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

Reduced hepatic function–Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 20 mg is the recommended dose for most hepatically impaired patients (see Dosage and Administration).

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

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2E1, but did suggest that it is a weak inhibitor of CYP-1A2, -2D6, and -2C19. Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. However, *in vivo* data to address this question are limited.

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

Clinical Efficacy Trials
The efficacy of Celexa as a treatment for depression was established in two placebo-controlled studies (of 4 to 6 weeks in duration) in adult outpatients (ages 18-66) meeting DSM-III or DSM-III-R criteria for major depression. Study 1, a 6-week trial in which patients received fixed Celexa doses of 10, 20, 40, and 60 mg/day, showed that Celexa at doses of 40 and 60 mg/day was effective as measured by the Hamilton Depression Rating Scale (HAMD) total score, the HAMD depressed mood item (Item 1), the Montgomery Asberg Depression Rating Scale, and the Clinical Global Impression (CGI) Severity scale. This study showed no clear effect of the 10 and 20 mg/day doses, and the 60 mg/day dose was not more effective than the 40 mg/day dose. In study 2, a 4-week, placebo-controlled trial in depressed patients, of whom 85% met criteria for melancholia, the initial dose was 20 mg/day, followed by titration to the maximum tolerated dose or a maximum dose of 80 mg/day. Patients treated with Celexa showed significantly greater improvement than placebo patients on the HAMD total score, HAMD item 1, and the CGI Severity score. In three additional placebo-controlled depression trials, the difference in response to treatment between patients receiving Celexa and patients receiving placebo was not statistically significant, possibly due to high spontaneous response rate, smaller sample size, or, in the case of one study, too low a dose.
In two long-term studies, depressed patients who had responded to Celexa during an initial 6 or 8 weeks of acute treatment (fixed doses of 20 or 40 mg/day in one study and flexible doses of 20-60 mg/day in the second study) were randomized to continuation of Celexa or to placebo. In both studies, patients receiving continued Celexa treatment experienced significantly lower relapse rates over the subsequent 6 months compared to those receiving placebo. In the fixed dose study, the decreased rate of depression relapse was similar in patients receiving 20 or 40 mg/day of Celexa. Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.
Comparison of Clinical Trial Results
Highly variable results have been seen in the clinical development of all antidepressant drugs. Furthermore, in those circumstances when the drugs have not been studied in the same controlled clinical trial(s), comparisons among the results of studies evaluating the effectiveness of different antidepressant drug products are inherently unreliable. Because conditions of testing (e.g., patient samples, investigators, doses of the treatments administered and compared, outcome measures, etc.) vary among trials, it is virtually impossible to distinguish a difference in drug effect from a difference due to one of the confounding factors just enumerated.

INDICATIONS AND USAGE
Celexa (citalopram HBr) is indicated for the treatment of depression.
The efficacy of Celexa in the treatment of depression was established in 4-6 week controlled trials of outpatients whose diagnosis corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder (see Clinical Pharmacology).
A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.
The antidepressant action of Celexa in hospitalized depressed patients has not been adequately studied.
The efficacy of Celexa in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials (see Clinical Pharmacology). Nevertheless, the physician who elects to use Celexa for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Concomitant use in patients taking monoamine oxidase inhibitors (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 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 Celexa 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 Celexa before starting a 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 premarketing testing. However, the electrocardiograms of 1116 patients who received Celexa in clinical trials were evaluated and the data indicate that Celexa is not associated with the development of clinically significant ECG abnormalities.

In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Celexa in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (see Dosage and Administration).
Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Celexa, however, it should be used with caution in such patients (see Dosage and Administration).
Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe Celexa.
Although in controlled studies Celexa has not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking or motor skills, and so patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities.
Patients should be told that, although Celexa has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Celexa and alcohol in depressed patients is not advised.
Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.
Patients should be 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 Celexa therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.
Laboratory Tests
There are no specific laboratory tests recommended.
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 (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised.
Warfarin – Administration of 40 mg/day Celexa for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.
Carbamazepine – Combined administration of Celexa (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered.
Triazolam – Combined administration of Celexa (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.
Ketoconazole – Combined administration of Celexa (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.
CYP3A4 and 2C19 Inhibitors – *In vitro* studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance.
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.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Citalopram was administered in the diet to NMRI/BOM strain mice and COBS Wl strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of citalopram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended human daily dose (MRHD) of 60 mg on a surface area (mg/m²) basis. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, respectively, on a mg/m² basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.
Mutagenesis
Citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.
Impairment of Fertility
When citalopram was administered orally to 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, approximately 5 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m²) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.
Pregnancy
Pregnancy Category C
In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose, which is approximately 18 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. This dose was also associated with maternal toxicity (clinical signs, decreased BW gain). The developmental no effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m^2 basis. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of up to 16 mg/kg/day, or approximately 5 times the MRHD on a mg/m^2 basis. Thus, teratogenic effects were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose, which is approximately 5 times the MRHD on a mg/m^2 basis. The no effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m^2 basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥24 mg/kg/day, approximately 4 times the MRHD on a mg/m^2 basis. A no effect dose was not determined in that study.

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

Labor and Delivery

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

Nursing Mothers

As has been found to occur with many other drugs, citalopram is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with 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 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 (see Dosage and Administration).

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

20 mg/day is the recommended dose for most elderly patients (see Dosage and Administration).

ADVERSE REACTIONS

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

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

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

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

Adverse Events Associated with Discontinuation of Treatment

Among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (i.e., associated with discontinuation in at least 1% of Celexa-treated patients at a rate at least twice that of placebo) are shown in TABLE 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	**Citalopram (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 on placebo ≥ Celexa: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.

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

[2]Primarily ejaculatory delay.

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

Dose Dependency of Adverse Events

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

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that 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.

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 SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Celexa and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clini-

cally 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:* bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration.

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

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

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

*% based on female subjects only: 2955

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

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

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

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

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

It is estimated that approximately 8 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 in at least 3 patients (unless otherwise noted) and are not described elsewhere in labeling: angioedema, choreoathetosis, epidermal necrolysis (3 cases), erythema multiforme, hepatic necrosis (2 cases), neuroleptic malignant syndrome, pancreatitis, serotonin syndrome, spontaneous abortion, thrombocytopenia, ventricular arrhythmia, Torsades de pointes, priapism, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Celexa (citalopram HBr) is not a controlled substance.

Physical and Psychological Dependence

Animal studies suggest that the abuse liability of Celexa is low. Celexa has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Celexa did not reveal any drug seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

Consequently, physicians should carefully evaluate Celexa patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE

Human Experience

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 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, 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).

Management of Overdose

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

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

DOSAGE AND ADMINISTRATION

Initial Treatment

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

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

Special Populations

20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients.

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

Maintenance Treatment

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

Switching Patients To or From a Monoamine Oxidase Inhibitor

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

HOW SUPPLIED

Tablets:

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

Beige, oval, film coated.
Imprint on one side with "FP". Imprint on the other side with "10 mg".

20 mg	Bottle of 100	NDC # 0456-4020-01
	10 x 10 Unit Dose	NDC # 0456-4020-63

Pink, oval, scored film coated.
Imprint on scored side with "F" on the left side and "P" on the right side.
Imprint on the non-scored side with "20 mg".

40 mg	Bottle of 100	NDC # 0456-4040-01
	10 x 10 Unit Dose	NDC # 0456-4040-63

White, oval, scored film coated.
Imprint on scored side with "F" on the left side and "P" on the right side.
Imprint on the non-scored side with "40 mg".

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

ANIMAL TOXICOLOGY

Retinal Changes in Rats

Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day (13 times the maximum recommended daily human dose of 60 mg on a mg/m² basis). Similar findings were not present in rats receiving 24 mg/kg/day for two years, in mice treated for 18 months at doses up to 240 mg/kg/day or in dogs treated for one year at doses up to 20 mg/kg/day (4, 20 and 10 times, respectively, the maximum recommended daily human dose on a mg/m² basis). Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

Cardiovascular Changes in Dogs

In a one-year toxicology study, 5 of 10 beagle dogs receiving oral doses of 8 mg/kg/day (4 times the maximum recommended daily human dose of 60 mg on a mg/m² basis) died suddenly between weeks 17 and 31 following initiation of treatment. Although appropriate data from that study are not available to directly compare plasma levels of citalopram (CT) and its metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), to levels that have been achieved in humans, pharmacokinetic data indicate that the relative dog to human exposure was greater for the metabolites than for citalopram. Sudden deaths were not observed in rats at doses up to 120 mg/kg/day, which produced plasma levels of CT, DCT and DDCT similar to those observed in dogs at doses of 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs. This effect occurred in dogs at doses producing peak DDCT plasma levels of 810 to 3250 nM (39-155 times the mean steady state DDCT plasma level measured at the maximum recommended human daily dose of 60 mg). In dogs, peak DDCT plasma concentrations are approximately equal to peak CT plasma concentrations, whereas in humans, steady state DDCT plasma concentrations are less than 10% of steady state CT plasma concentrations. Assays of DDCT plasma concentrations in 2,020 citalopram treated individuals demonstrated that DDCT levels rarely exceeded 70 nM; the highest measured level of DDCT in human overdose was 138 nM. While DDCT is ordinarily present in humans at lower levels than in dogs, it is unknown whether there are individuals who may achieve higher DDCT levels. The possibility that DCT, a principal metabolite in humans, may prolong the QT interval in the dog has not been directly examined because DCT is rapidly converted to DDCT in that species.

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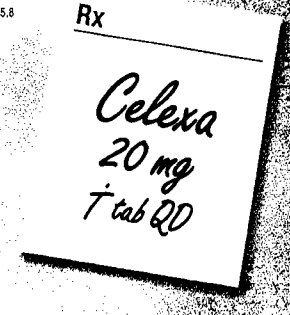
citalopram HBr™

Effective first-line SSRI therapy with a
favorable side-effect profile

- Incidence of insomnia, anxiety, agitation, and nervousness comparable to placebo[1]
- Incidence of fatigue comparable to placebo
- Not associated with clinically significant weight changes[5,8]
- Efficacy proven in the treatment of depression
- More than 12 years of worldwide use in over 30 million patients[1]
- Widely available on managed care formularies[1]
- Available in oral solution and 10 mg tablets for more flexible dosing



The most frequent adverse events reported with CELEXA vs placebo in clinical trials were nausea (21% vs 14%), dry mouth (20% vs 14%), somnolence (18% vs 10%), insomnia (15% vs 14%), increased sweating (11% vs 9%), tremor (8% vs 6%), diarrhea (8% vs 5%), and ejaculation disorder (6% vs 1%).

CELEXA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients with a hypersensitivity to citalopram HBr or any of the ingredients in CELEXA.

Visit the CELEXA Website at http://www.CELEXA.com

For complete details about contraindications, warnings, precautions, adverse reactions, and dosage and administration, please see full prescribing information.

Celexa™
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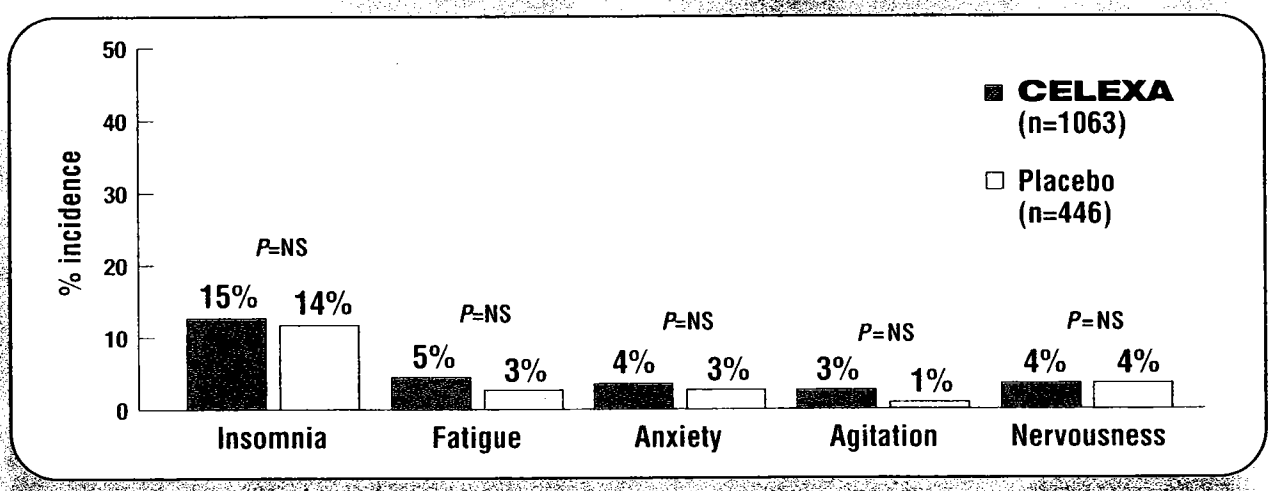
FOR DEPRESSION

Celexa

Favorable side-effect profile

*In short-term clinical trials**

No statistically significant insomnia, fatigue, anxiety, agitation, or nervousness vs placebo[1]



GI side effects vs placebo[1]

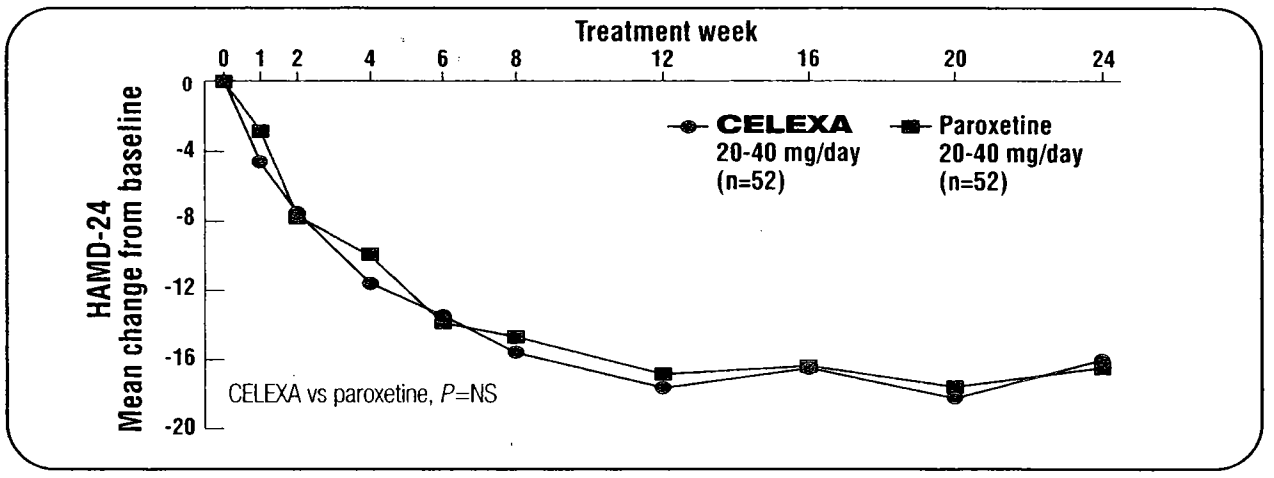
	Constipation	Diarrhea	Dyspepsia	Nausea	Vomiting
CELEXA (n=1063)	9%	8%	5%	21%	4%
Placebo (n=446)	9%	5%	4%	14%	3%

Celexa

Effectively treats major depression

In a 6-month clinical trial

CELEXA 20-40 mg/day and paroxetine 20-40 mg/day effectively treated major depression[4]



Study design: 24-week, double-blind, randomized, parallel, flexible-dose study (CELEXA 20-40 mg/day; paroxetine 20-40 mg/day) U.S. multicenter trial in 104 patients with depression and associated anxiety (HAMD-24 ≥18 and HAMA ≥17 at baseline). Baseline HAMD-24 mean total score: CELEXA, 29.33; paroxetine, 29.67. Mean daily dose for CELEXA was 27.4 mg/day and for paroxetine 28.6 mg/day.

- CELEXA and paroxetine both produced clinically significant reductions in major depression at similar doses (mean daily dose 27.4 mg/day and 28.6 mg/day, respectively)[4]

Source: Jefferson JW, Greist JH. Presented at the 39th Annual Meeting, American College of Neuropsychopharmacology, Dec 2000.

weight change

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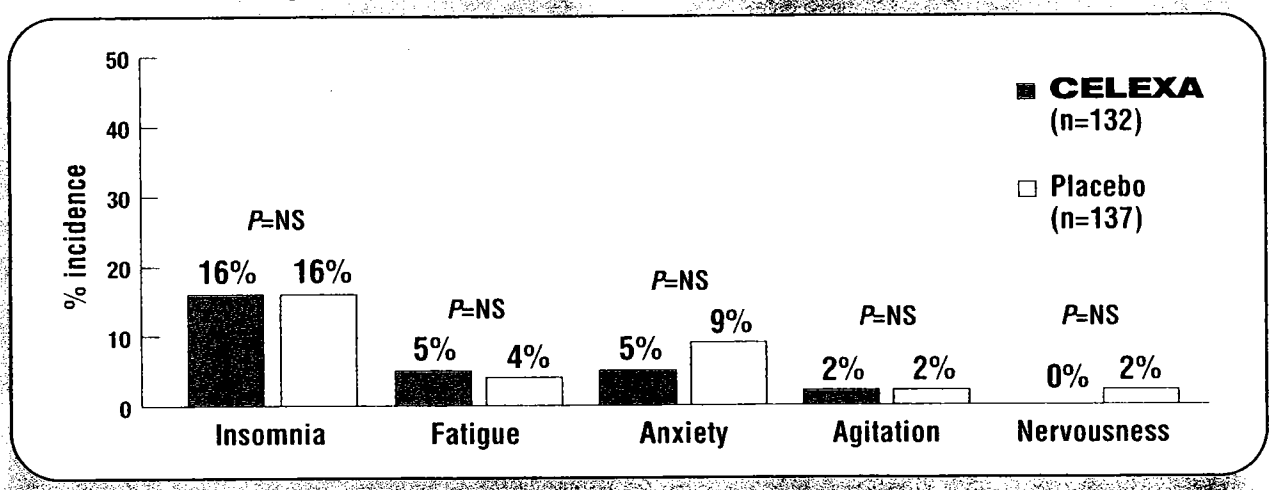
Well-tolerated SSRI therapy

Celexa

Favorable side-effect profile in long-term treatment

*In a long-term clinical trial**

No statistically significant insomnia, fatigue, anxiety, agitation, or nervousness vs placebo[1]



GI side effects vs placebo[1]

	Constipation	Diarrhea	Dyspepsia	Nausea	Vomiting
CELEXA (n=132)	2%	4%	2%	6%	5%
Placebo (n=137)	2%	2%	3%	10%	3%

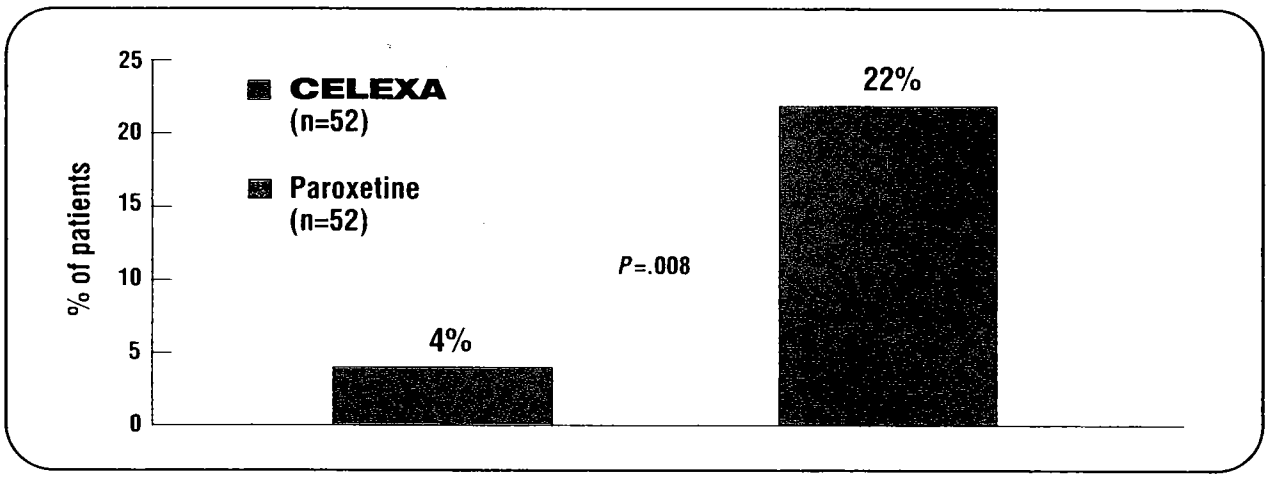
- CELEXA has a favorable side-effect profile across treatment types in long-term treatment (up to 6 months)

Celexa

Low incidence of weight gain in long-term treatment

In a 6-month trial

Significantly fewer patients treated with CELEXA 20-40 mg/day experienced weight gain vs paroxetine 20-40 mg/day[4]



Study design: 6-month, double-blind, randomized, parallel, flexible-dose (CELEXA 20-40 mg/day; paroxetine 20-40 mg/day) U.S. multicenter trial in 104 patients with anxious depression. Mean daily dose for CELEXA was 27.4 mg/day and for paroxetine, 28.6 mg/day. Significant weight gain is defined as ≥7% increase in weight.

- Only 4% of CELEXA-treated patients experienced significant weight gain vs 22% of patients treated with paroxetine[4]

Source: Jefferson JW, Greist JH. Presented at the 39th Annual Meeting, American College of Neuropsychopharmacology, Dec 2000.

In a separate study

CELEXA was not associated with clinically significant long-term weight changes[6]

- CELEXA therapy was associated with a mean weight increase of only 1.5 kg after 12 months[6]

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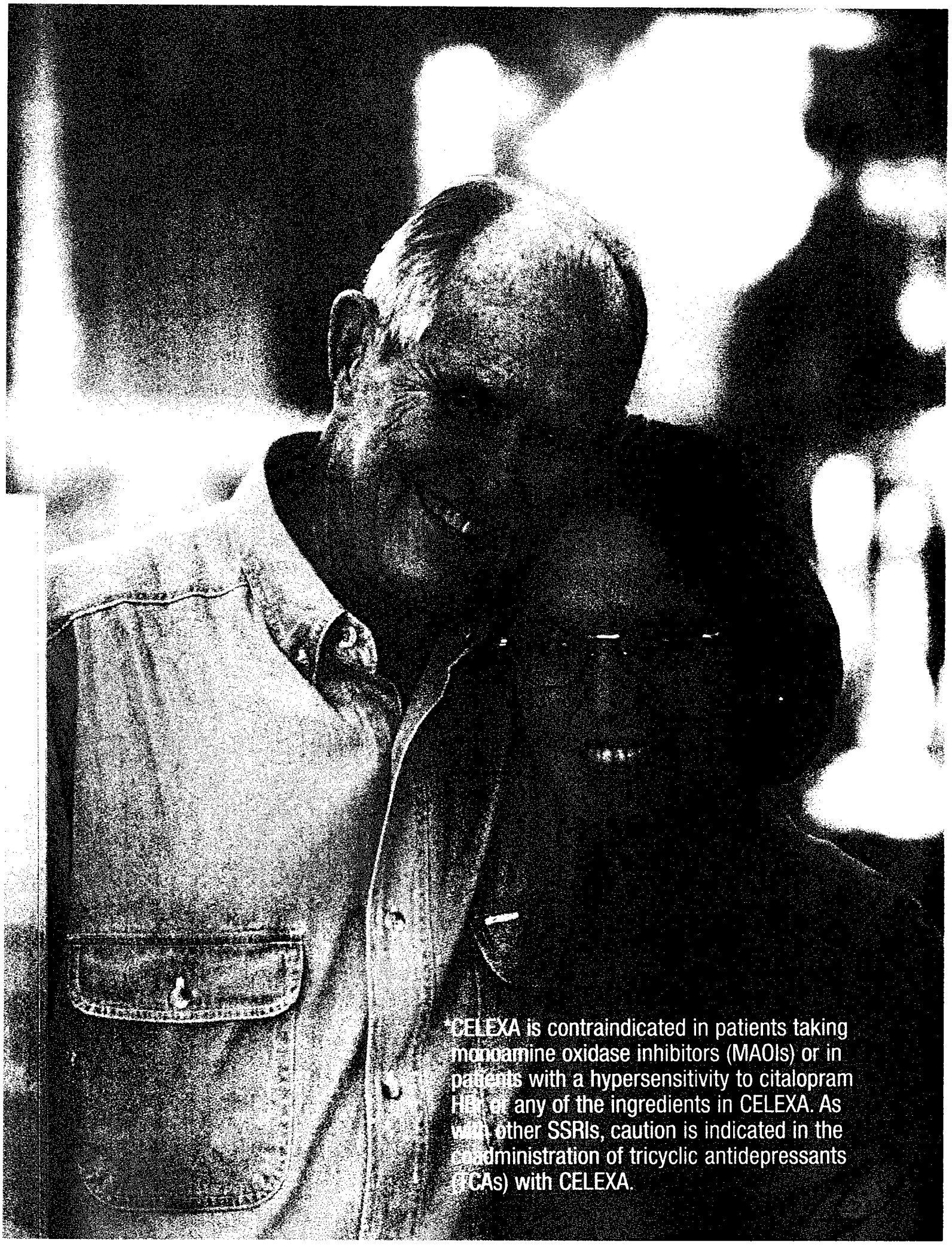
Well-tolerated SSRI therapy



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

Celexa

Does not interfere with the metabolism of many drugs*[1,7]

P450 isozyme inhibition by SSRIs *in vitro*[7]

	Isozymes				
	3A4†	2D6	1A2	2C19	2C9
CELEXA	0	+	+	0	0
Fluoxetine	++	+++	+	++	++
Paroxetine	+	+++	+	+	+
Sertraline	+	+	+	++	+

0 = minimal or zero inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = strong inhibition.

Source: Greenblatt DJ, et al. *J Clin Psychiatry.* 1998;59(suppl 15):19-27.

- CELEXA does not inhibit CYP3A4 and CYP2C9 *in vitro*[7]
- CELEXA is a weak inhibitor of CYP2D6, CYP1A2, and CYP2C19[7]

*The clinical significance of *in vitro* data is unknown.

†*In vitro* enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, and CELEXA would be expected to have little inhibitory effect on *in vivo* metabolism by this enzyme. *In vivo* data demonstrating a lack of this effect are limited to carbamazepine and warfarin.

No dosage adjustment recommended with:

- Digoxin
- Warfarin
- Cimetidine
- Carbamazepine
- Theophylline[1]

May be used with highly protein-bound drugs

- Low plasma protein binding (approximately 80%) *in vitro*

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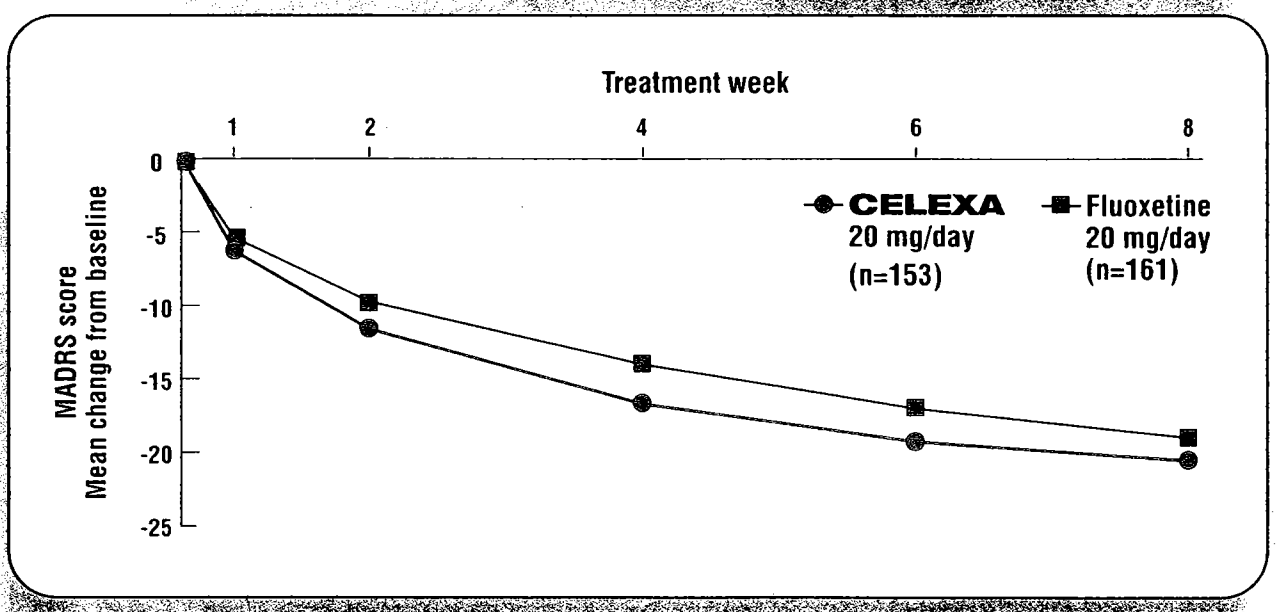
Efficacy comparable to fluoxetine

In a head-to-head clinical trial

CELEXA 20 mg/day and fluoxetine 20 mg/day effectively treated major depression[8]



Study design: 8-week, double-blind, randomized, parallel, fluoxetine-controlled, fixed-dose (20 mg/day) study in patients with major depression (MADRS ≥ 22). Baseline MADRS: CELEXA: 29.7; fluoxetine: 29.4

- There was no statistical difference between CELEXA 20 mg and fluoxetine 20 mg at week 8

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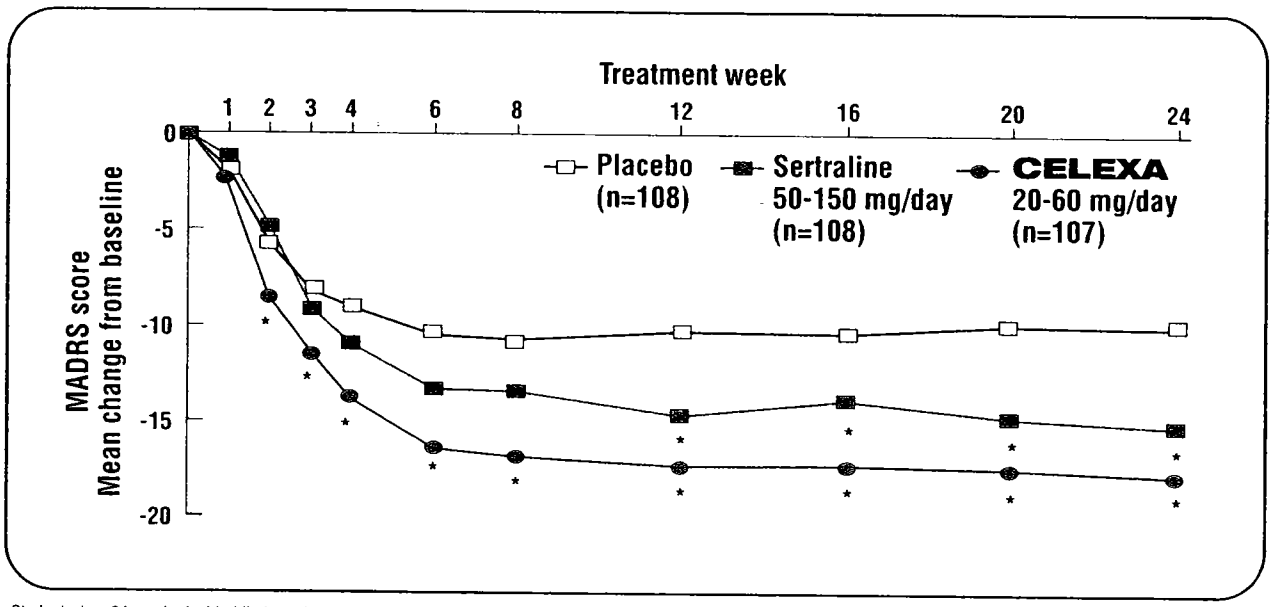
Efficacy comparable to sertraline

In a 6-month trial

CELEXA 20-60 mg/day and sertraline 50-150 mg/day effectively treated moderate to severe depression[9]



Study design: 24-week, double-blind, randomized, parallel, placebo-controlled, flexible-dose (CELEXA, 20-60 mg/day; sertraline, 50-150 mg/day), U.S. multicenter trial in patients with major depression. Baseline MADRS mean total score: placebo, 31.1; CELEXA, 32.4; sertraline, 31.2.

*Significantly different from placebo ($P<.05$).

- CELEXA and sertraline both significantly improved depression at week 24 compared with placebo ($P<.05$)[9]

Source: Stahl SM. *Biol Psychiatry*. 2000;48:894-901.

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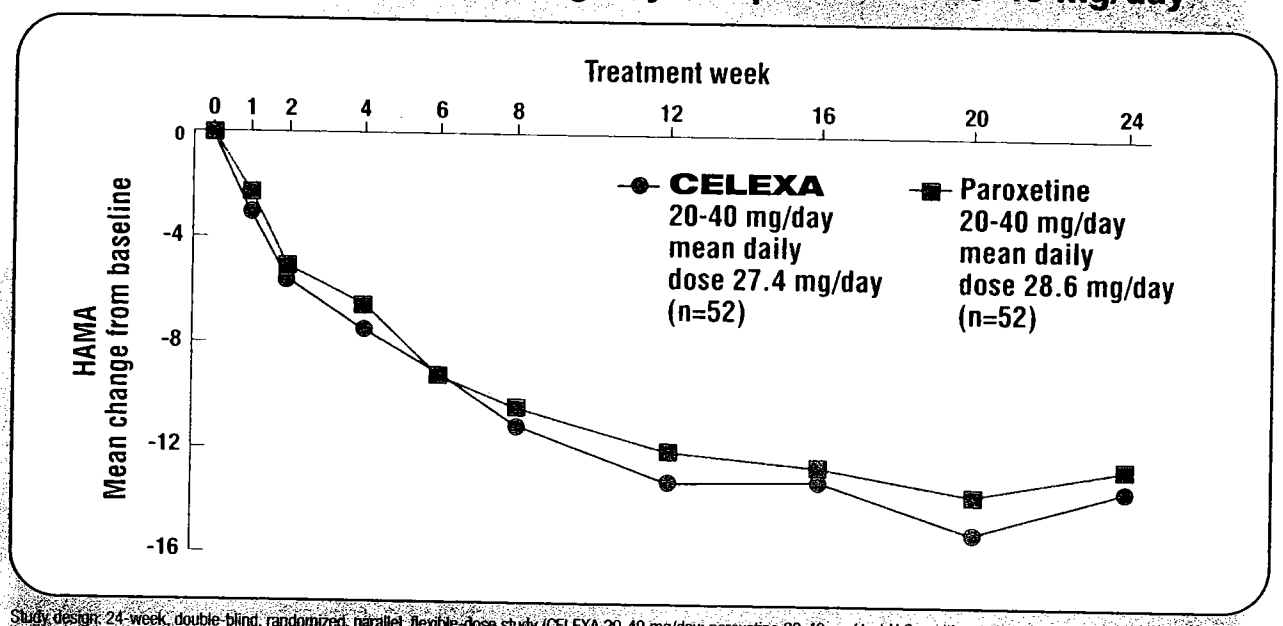
CELEXA and paroxetine both significantly reduced anxiety symptoms associated with depression[4]

Clinical trial of CELEXA 20-40 mg/day and paroxetine 20-40 mg/day[4]



Study design: 24-week, double-blind, randomized, parallel, flexible-dose study (CELEXA 20-40 mg/day; paroxetine 20-40 mg/day) U.S. multicenter trial in 104 patients with depression and associated anxiety (HAMD-24 ≥18 and HAMA ≥17 at baseline). Baseline HAMA mean total score: CELEXA, 23.02; paroxetine, 22.20. Mean daily dose for CELEXA was 27.4 mg/day and for paroxetine 28.6 mg/day.

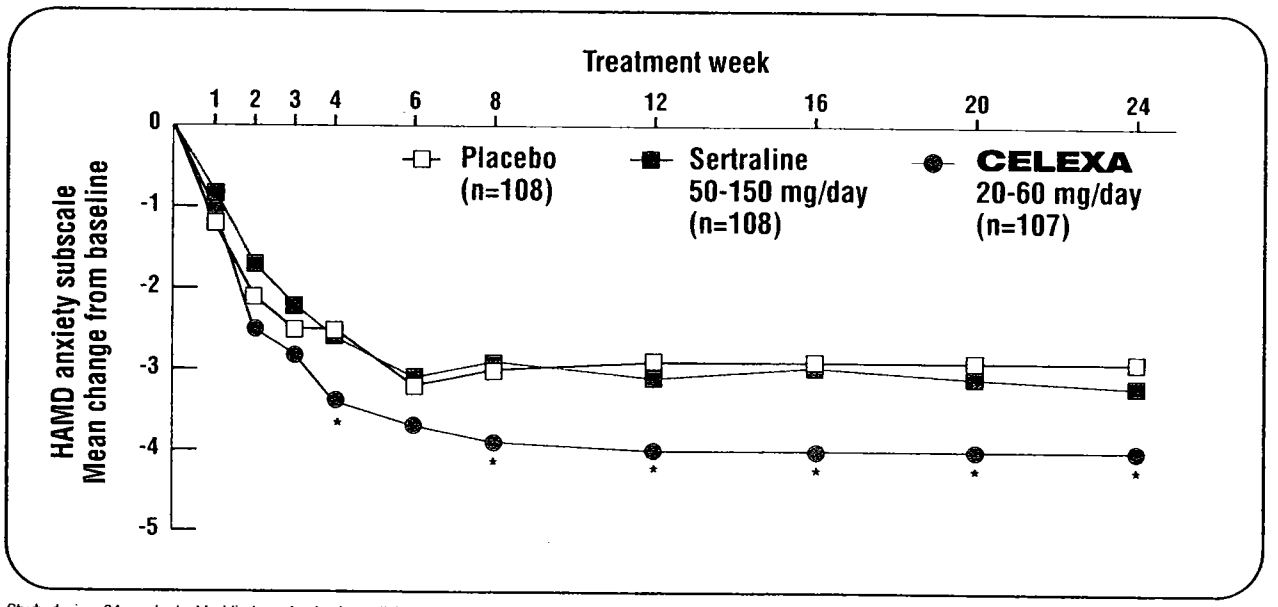
- CELEXA and paroxetine both produced clinically significant reductions in anxiety symptoms at similar doses (mean daily dose 27.4 mg/day and 28.6 mg/day, respectively)[4]

[4] Data on file. JW Crest-81. Presented at the 36th Annual Meeting American College of Neuropsychopharmacology, December [illegible]

Celexa

Effectively treats anxiety symptoms in depressed patients

Clinical trial of CELEXA 20-60 mg/day and sertraline 50-150 mg/day vs placebo[9]

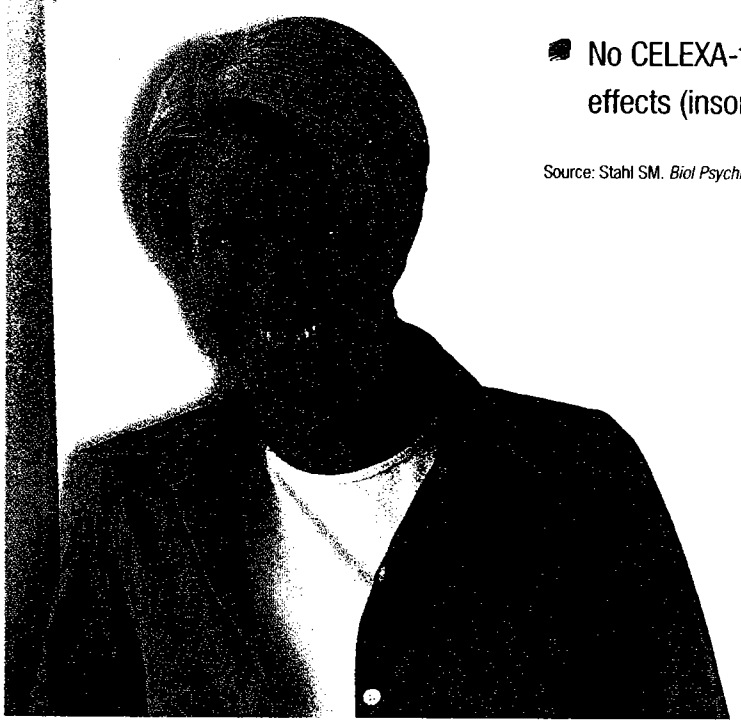


Study design: 24-week, double-blind, randomized, parallel, placebo-controlled, flexible-dose (CELEXA, 20-60 mg/day; sertraline, 50-150 mg/day), U.S. multicenter trial in patients with major depression. Baseline HAMD anxiety subscale mean total score: placebo, 7.9; CELEXA, 7.9; sertraline, 7.7.

*Significantly different from placebo ($P<.01$).

- CELEXA significantly reduced anxiety symptoms in depressed patients vs placebo[9]
- No CELEXA-treated patient discontinued due to activating side effects (insomnia, agitation, anxiety, nervousness)[9]

Source: Stahl SM. *Biol Psychiatry*. 2000;48:894-901.



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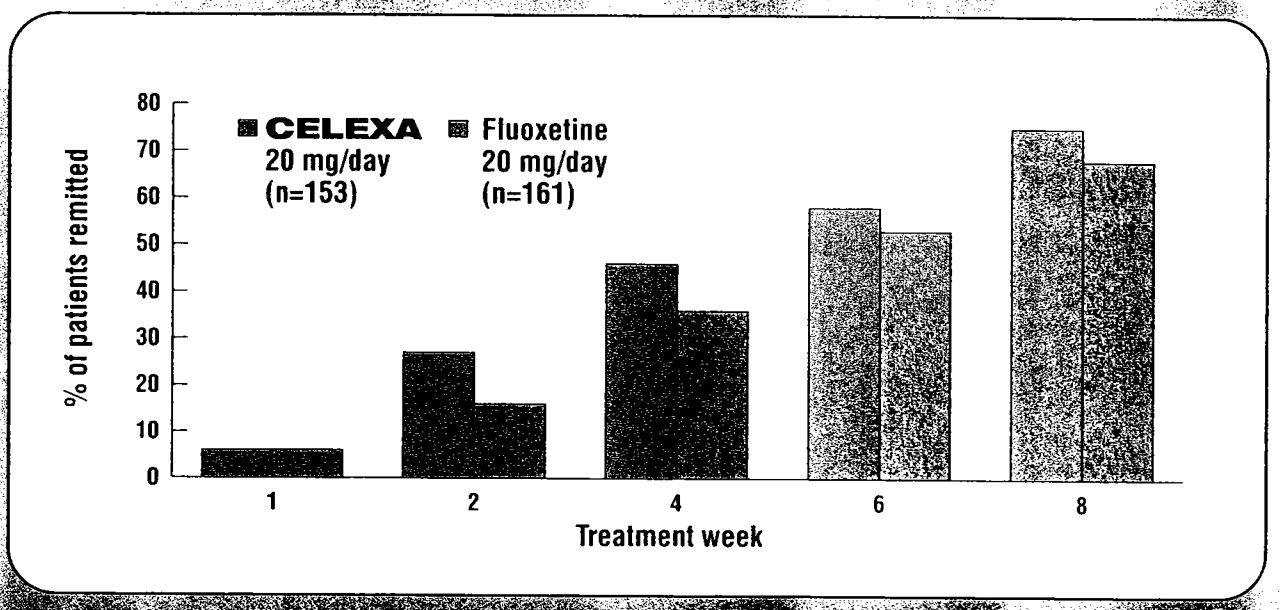
Effectively achieves remission in short-term treatment

In a short-term clinical study

Remission rates of CELEXA 20 mg/day and fluoxetine 20 mg/day*[10]



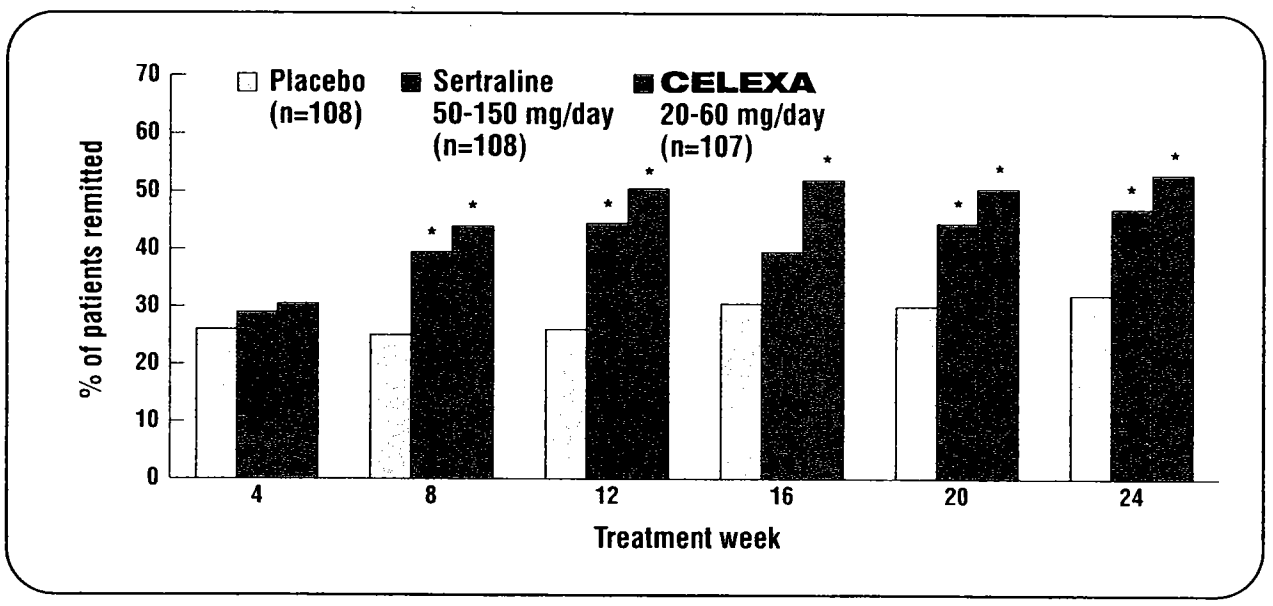
8-week, double-blind, randomized, parallel-group, fixed dose (20 mg/day) study in patients with major depressive disorder (MADRS ≥22). Baseline MADRS scores were comparable between treatment groups.

Celexa

Effectively achieves remission in long-term treatment

In a 6-month trial

More CELEXA patients had a full remission of their depressive symptoms compared with placebo[1,9]



Study design: 24-week, double-blind, randomized, parallel, placebo-controlled, flexible-dose, U.S. multicenter trial in patients with major depression. Baseline MADRS mean total score: placebo, 31.1; CELEXA, 32.4; sertraline, 31.2.

*Significantly different from placebo ($P<.05$).

- In this study, remission is defined as MADRS total score ≤12[9]
- Over 60% more CELEXA-treated patients achieved remission at endpoint compared with placebo[1,9]

Source: Stahl SM. *Biol Psychiatry*. 2000;48:894-901.

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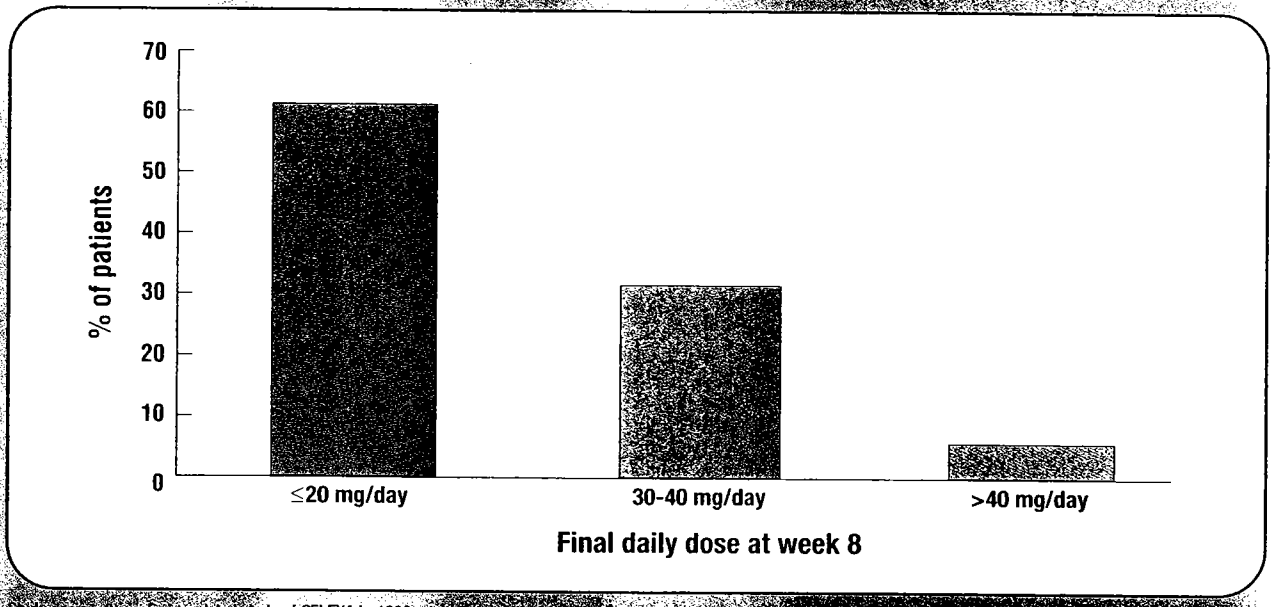
Effective 20 mg starting dose

In a large U.S. multicenter trial

Most CELEXA-treated patients remained on the initial 20 mg/day starting dose[1]



Study design: 8-week, open-label study of CELEXA in 1333 adult patients (18 years of age) with major depressive [illegible] could be increased in 20 mg increments, to a maximum of 60 mg/day [illegible] for any patient who [illegible]

- Overall, mean daily dose was [illegible]
- More than 60% of the patients [illegible] were maintained on [illegible] and experienced [illegible]
- [illegible] were titrated [illegible]
- [illegible] responders [illegible]

Celexa

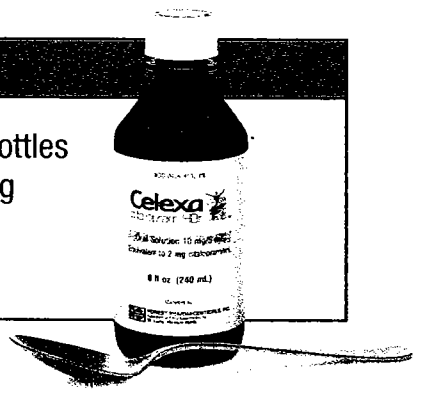
Convenient QD dosing

Once-daily 20 mg starting dose for all patients[11]

- Initial dose of 20 mg once daily, generally with an increase to 40 mg once daily
- Doses of more than 40 mg are not ordinarily necessary
- Dose increases should occur in 20 mg increments at intervals of no less than 1 week
- May be taken any time of day with or without food
- Available in 10 mg tablets for more flexible dosing

CELEXA is available in two forms

Tablets	Oral solution
10 mg 	8-ounce (240 mL) bottles 1 tsp contains 10 mg — sugar free — alcohol free
20 mg 	
40 mg 	



20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients.

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References

1. Data on file, Forest Laboratories, Inc.

2. Prescription Audit 2000, NDC Health Information Services.

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4. Jefferson JW, Greist JH. A double-blind comparison of citalopram and paroxetine in the treatment of patients with depression and anxiety. Presented at the 39th Annual Meeting, American College of Neuropsychopharmacology; 2000; San Juan, Puerto Rico.

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9. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry*. 2000;48:894-901.

10. Patris M, Bouchard J-M, Bougerol T, et al. Citalopram versus fluoxetine: a double-blind, controlled, multicentre phase III trial in patients with unipolar major depression treated in general practice. *Int Clin Psychopharmacol*. 1996;11:129-136.

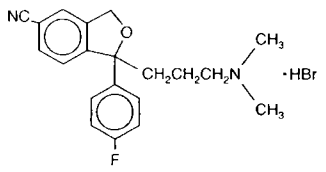
11. Montgomery SA, Pedersen V, Tanghøj P, Rasmussen C, Bjerg P. The optimal dosage regimen for citalopram: meta-analysis of nine placebo-controlled studies. *Int Clin Psychopharmacol*. 1994;9(suppl 1):35-40.

12. Lyby K, Elsborg L, Høpfner Petersen HE, Skovlund E. Long-term safety of citalopram. Abstract presented at the CINP Congress; 1988; Munich.

Celexa™
citalopram HBr

DESCRIPTION

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



The molecular formula is $C_{20}H_{22}BrFN_2O$ and its molecular weight is 405.35.
Citalopram HBr occurs as a fine white to off-white powder. Citalopram HBr is sparingly soluble in water and soluble in ethanol.
Celexa (citalopram hydrobromide) is available as tablets or as an oral solution.
Celexa 10 mg tablets are film coated, oval tablets containing citalopram HBr in strengths equivalent to 10 mg citalopram base. Celexa 20 mg and 40 mg tablets are film coated, oval, scored tablets containing citalopram HBr in strengths equivalent to 20 mg or 40 mg citalopram base. The tablets also contain the following inactive ingredients: Copolyvidone, Corn Starch, Crosscarmellose Sodium, Glycerin, Lactose Monohydrate, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Microcrystalline Cellulose, Polyethylene Glycol, and Titanium Dioxide. Iron Oxides are used as coloring agents in the beige (10 mg) and pink (20 mg) tablets.
Celexa oral solution contains citalopram HBr equivalent to 2mg/mL citalopram base. It also contains the following inactive ingredients: Sorbitol, Purified Water, Propylene Glycol, Methylparaben, Natural Peppermint Flavor, and Propylparaben.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that citalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long term (14 day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer. Citalopram has no or very low affinity for 5-HT_{1A}, 5-HT_{2A}, dopamine D_1 and D_2, α_1-, α_2-, and β-adrenergic, histamine H_1, gamma aminobutyric acid (GABA), muscarinic, cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular effects of other psychotropic drugs.

Pharmacokinetics

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

Absorption and Distribution

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

Metabolism and Elimination

Following intravenous administrations of citalopram, the fraction of drug recovered in the urine as citalopram and DCT was about 10% and 5%, respectively. The systemic clearance of citalopram was 330 mL/min, with approximately 20% of that due to renal clearance.
Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide and a deaminated propionic acid derivative. In humans, unchanged citalopram is the predominant compound in plasma. At steady state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram.
In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram.

Population Subgroups

Age – Citalopram pharmacokinetics in subjects ≥60 years of age were compared to younger subjects in two normal volunteer studies. In a single dose study, citalopram AUC and half-life were increased in the elderly subjects by 30% and 50%, respectively, whereas in a multiple dose study they were increased by 23% and 30%, respectively. 20 mg is the recommended dose for most elderly patients (see Dosage and Administration).
Gender – In three pharmacokinetic studies (total N=32), citalopram AUC in women was one and a half to two times that in men. This difference was not observed in five other pharmacokinetic studies (total N=114). In clinical studies, no differences in steady state serum citalopram levels were seen between men (N=237) and women (N=388). There were no gender differences in the pharmacokinetics of DCT and DDCT. No adjustment of dosage on the basis of gender is recommended.
Reduced hepatic function – Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 20 mg is the recommended dose for most hepatically impaired patients (see Dosage and Administration).
Reduced renal function – In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of citalopram in patients with severely reduced renal function (creatinine clearance <20 mL/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2E1, but did suggest that it is a weak inhibitor of CYP-1A2, -2D6, and -2C19. Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. However, *in vivo* data to address this question are limited.
Since CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of 3A4, e.g., ketoconazole, itraconazole, and macrolide antibiotics, and potent inhibitors of CYP2C19, e.g., omeprazole, might decrease the clearance of citalopram. However, coadministration of citalopram and the potent 3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple dose administration of Celexa, suggesting that coadministration, with Celexa, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on citalopram metabolism. See Drug Interactions under Precautions for more detailed information on available drug interaction data.

Clinical Efficacy Trials

The efficacy of Celexa as a treatment for depression was established in two placebo-controlled studies (of 4 to 6 weeks in duration) in adult outpatients (ages 18-66) meeting DSM-III or DSM-III-R criteria for major depression. Study 1, a 6-week trial in which patients received fixed Celexa doses of 10, 20, 40, and 60 mg/day, showed that Celexa at doses of 40 and 60 mg/day was effective as measured by the Hamilton Depression Rating Scale (HAMD) total score, the HAMD depressed mood item (item 1), the Montgomery Asberg Depression Rating Scale, and the Clinical Global Impression (CGI) Severity scale. This study showed no clear effect of the 10 and 20 mg/day doses, and the 60 mg/day dose was not more effective than the 40 mg/day dose. In study 2, a 4-week, placebo-controlled trial in depressed patients, of whom 85% met criteria for melancholia, the initial dose was 20 mg/day, followed by titration to the maximum tolerated dose or a maximum dose of 80 mg/day. Patients treated with Celexa showed significantly greater improvement than placebo patients on the HAMD total score, HAMD item 1, and the CGI Severity score. In three additional placebo-controlled depression trials, the difference in response to treatment between patients receiving Celexa and patients receiving placebo was not statistically significant, possibly due to high spontaneous response rate, smaller sample size, or, in the case of one study, too low a dose.
In two long-term studies, depressed patients who had responded to Celexa during an initial 6 or 8 weeks of acute treatment (fixed doses of 20 or 40 mg/day in one study and flexible doses of 20-60 mg/day in the second study) were randomized to continuation of Celexa or to placebo. In both studies, patients receiving continued Celexa treatment experienced significantly lower relapse rates over the subsequent 6 months compared to those receiving placebo. In the fixed dose study, the decreased rate of depression relapse was similar in patients receiving 20 or 40 mg/day of Celexa. Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

Comparison of Clinical Trial Results

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

INDICATIONS AND USAGE

Celexa (citalopram HBr) is indicated for the treatment of depression.
The efficacy of Celexa in the treatment of depression was established in 4-6 week controlled trials of outpatients whose diagnosis corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder (see Clinical Pharmacology).
A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.
The antidepressant action of Celexa in hospitalized depressed patients has not been adequately studied.
The efficacy of Celexa in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials (see Clinical Pharmacology). Nevertheless, the physician who elects to use Celexa for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (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 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 Celexa 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 Celexa before starting a 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 premarketing testing. However, the electrocardiograms of 1116 patients who received Celexa in clinical trials were evaluated and the data indicate that Celexa is not associated with the development of clinically significant ECG abnormalities.
In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Celexa in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (see Dosage and Administration).
Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Celexa, however, it should be used with caution in such patients (see Dosage and Administration).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Celexa.
Although in controlled studies Celexa has not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking or motor skills, and so patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities.
Patients should be told that, although Celexa has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Celexa and alcohol in depressed patients is not advised.
Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.
Patients should be 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 Celexa therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Laboratory Tests
There are no specific laboratory tests recommended.

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 (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised.
Warfarin – Administration of 40 mg/day Celexa for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.
Carbamazepine – Combined administration of Celexa (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered.
Triazolam – Combined administration of Celexa (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.
Ketoconazole – Combined administration of Celexa (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.
CYP3A4 and 2C19 Inhibitors – *In vitro* studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance.
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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of citalopram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended human daily dose (MRHD) of 60 mg on a surface area (mg/m^2) basis. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, respectively, on a mg/m^2 basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.
Mutagenesis
Citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation.
Citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.
Impairment of Fertility
When citalopram was administered orally to 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, approximately 5 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.

Pregnancy
Pregnancy Category C
In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.
In two rat embryo/fetal development studies, oral administration of citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose, which is approximately 18 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. This dose was also associated with maternal toxicity (clinical signs, decreased BW gain). The developmental no effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m^2 basis.
In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of up to 16 mg/kg/day, or approximately 5 times the MRHD on a mg/m^2 basis. Thus, teratogenic effects were observed at a maternally toxic dose in the rat and were not observed in the rabbit.
When female rats were treated with citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose, which is approximately 5 times the MRHD on a mg/m^2 basis. The no effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m^2 basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥24 mg/kg/day, approximately 4 times the MRHD on a mg/m^2 basis. A no effect dose was not determined in that study.
There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers
As has been found to occur with many other drugs, citalopram is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with 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 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 (see Dosage and Administration).
In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively (see Clinical Pharmacology).
20 mg/day is the recommended dose for most elderly patients (see Dosage and Administration).

CELEXA™
(citalopram HBr)

ADVERSE REACTIONS
The premarketing development program for Celexa included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Celexa varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.
The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials
Adverse Events Associated with Discontinuation of Treatment
Among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (i.e., associated with discontinuation in at least 1% of Celexa-treated patients at a rate at least twice that of placebo) are shown in TABLE 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	**Citalopram (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 on placebo ≥ Celexa: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.
[1] Denominator used was for females only (N=638 Celexa; N=252 placebo).
[2] Primarily ejaculatory delay.
[3] Denominator used was for males only (N=425 Celexa; N=194 placebo).

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

Male and Female Sexual Dysfunction with SSRIs
Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that 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.
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 SSRIs, physicians should routinely inquire about such possible side effects.

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

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

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

ECG Changes
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:* bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration.
Musculoskeletal System Disorders–*Infrequent:* arthritis, muscle weakness, skeletal pain. *Rare:* bursitis, osteoporosis.
Psychiatric Disorders–*Frequent:* impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. *Infrequent:* increased libido, aggressive reaction, paroniria, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. *Rare:* catatonic reaction, melancholia.
Reproductive Disorders/Female*–*Frequent:* amenorrhea. *Infrequent:* galactorrhea, breast pain, breast enlargement, vaginal hemorrhage.
*% based on female subjects only: 2955
Respiratory System Disorders–*Frequent:* coughing. *Infrequent:* bronchitis, dyspnea, pneumonia. *Rare:* asthma, laryngitis, bronchospasm, pneumonitis, sputum increased.
Skin and Appendages Disorders–*Frequent:* rash, pruritus. *Infrequent:* photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. *Rare:* hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani.
Special Senses–*Frequent:* accommodation abnormal, taste perversion. *Infrequent:* tinnitus, conjunctivitis, eye pain. *Rare:* mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss.
Urinary System Disorders–*Frequent:* polyuria. *Infrequent:* micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare:* facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain.
Other Events Observed During the Non-US Postmarketing Evaluation of Celexa (citalopram HBr)
It is estimated that approximately 8 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 in at least 3 patients (unless otherwise noted) and are not described elsewhere in labeling: angioedema, choreoathetosis, epidermal necrolysis (3 cases), erythema multiforme, hepatic necrosis (2 cases), neuroleptic malignant syndrome, pancreatitis, serotonin syndrome, spontaneous abortion, thrombocytopenia, ventricular arrhythmia, Torsades de pointes, priapism, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
Celexa (citalopram HBr) is not a controlled substance.

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

OVERDOSAGE

Human Experience
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 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, 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).

Management of Overdose
Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of citalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Celexa.
In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment
Celexa (citalopram HBr) should be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of no less than one week. Although certain patients may require a dose of 60 mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.
Celexa should be administered once daily, in the morning or evening, with or without food.

Special Populations
20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients.
No dosage adjustment is necessary for patients with mild or moderate renal impairment. Celexa should be used with caution in patients with severe renal impairment.

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

Switching Patients To or From a Monoamine Oxidase Inhibitor
At least 14 days should elapse between discontinuation of an MAOI and initiation of Celexa therapy. Similarly, at least 14 days should be allowed after stopping Celexa before starting a MAOI (see Contraindications and Warnings).

HOW SUPPLIED

Tablets:

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

Beige, oval, film coated.
Imprint on one side with "FP". Imprint on the other side with "10 mg".

20 mg	Bottle of 100	NDC # 0456-4020-01
	10 x 10 Unit Dose	NDC # 0456-4020-63

Pink, oval, scored film coated.
Imprint on scored side with "F" on the left side and "P" on the right side.
Imprint on the non-scored side with "20 mg".

40 mg	Bottle of 100	NDC # 0456-4040-01
	10 x 10 Unit Dose	NDC # 0456-4040-63

White, oval, scored film coated.
Imprint on scored side with "F" on the left side and "P" on the right side.
Imprint on the non-scored side with "40 mg".

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

ANIMAL TOXICOLOGY

Retinal Changes in Rats
Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day (13 times the maximum recommended daily human dose of 60 mg on a mg/m² basis). Similar findings were not present in rats receiving 24 mg/kg/day for two years, in mice treated for 18 months at doses up to 240 mg/kg/day or in dogs treated for one year at doses up to 20 mg/kg/day (4, 20 and 10 times, respectively, the maximum recommended daily human dose on a mg/m² basis).
Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

Cardiovascular Changes in Dogs
In a one-year toxicology study, 5 of 10 beagle dogs receiving oral doses of 8 mg/kg/day (4 times the maximum recommended daily human dose of 60 mg on a mg/m² basis) died suddenly between weeks 17 and 31 following initiation of treatment. Although appropriate data from that study are not available to directly compare plasma levels of citalopram (CT) and its metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), to levels that have been achieved in humans, pharmacokinetic data indicate that the relative dog to human exposure was greater for the metabolites than for citalopram. Sudden deaths were not observed in rats at doses up to 120 mg/kg/day, which produced plasma levels of CT, DCT and DDCT similar to those observed in dogs at doses of 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs. This effect occurred in dogs at doses producing peak DDCT plasma levels of 810 to 3250 nM (39-155 times the mean steady state DDCT plasma level measured at the maximum recommended human daily dose of 60 mg). In dogs, peak DDCT plasma concentrations are approximately equal to peak CT plasma concentrations, whereas in humans, steady state DDCT plasma concentrations are less than 10% of steady state CT plasma concentrations. Assays of DDCT plasma concentrations in 2,020 citalopram treated individuals demonstrated that DDCT levels rarely exceeded 70 nM; the highest measured level of DDCT in human overdose was 138 nM. While DDCT is ordinarily present in humans at lower levels than in dogs, it is unknown whether there are individuals who may achieve higher DDCT levels. The possibility that DCT, a principal metabolite in humans, may prolong the QT interval in the dog has not been directly examined because DCT is rapidly converted to DDCT in that species.

Rx only

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

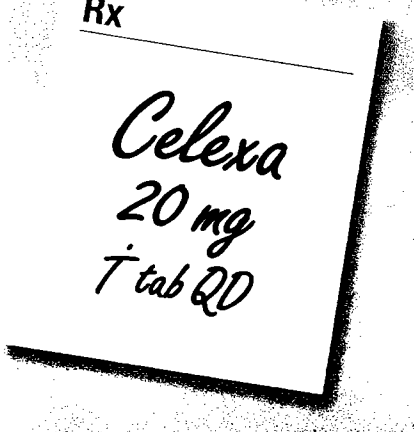
Licensed from H. Lundbeck A/S

Rev: 08/01

Celexa
citalopram HBr™

Effective first-line SSRI therapy with a
favorable side-effect profile

- Incidence of insomnia, anxiety, agitation, and nervousness comparable to placebo[1]
- Incidence of fatigue comparable to placebo
- Not associated with clinically significant weight changes[4,12]
- Efficacy proven in the treatment of depression
- More than 12 years of worldwide use in over 30 million patients[1]
- Widely available on managed care formularies[1]
- Available in oral solution and 10 mg tablets for more flexible dosing



The most frequent adverse events reported with CELEXA vs placebo in clinical trials were nausea (21% vs 14%), dry mouth (20% vs 14%), somnolence (18% vs 10%), insomnia (15% vs 14%), increased sweating (11% vs 9%), tremor (8% vs 6%), diarrhea (8% vs 5%), and ejaculation disorder (6% vs 1%).

CELEXA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) [illegible] patients with a hypersensitivity to citalopram HBr or any of the ingredients in CELEXA.

Visit the CELEXA Web site at http://www.CELEXA.com

[illegible]

For use by Forest Representatives only. Not to be left with physician.

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