Celexa® italopram hydrobromid Tablets/Oral Solution

### Rx Only

Suicidality in Children and Adolescents Antidagressants increased the risk of suicidal thinking and behavior faucidality in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders, Anyone considering the use of Celexo any and Uner antidepressant in a child or adolescent must balance this risk with the clinical need Patients Who we started on the raiks with the clinical head Patients Who we started on the raiks with the clinical adolescent rouge tabance this risk with the clinical adolescent rouge tabance this risk with the clinical adolescent regimes and the advised of the need for claws observations and communication with the prescriber. Claws is ond anonymous for uses in certainter, classes, filescents and the prescribers. Suicidality in Children and Adolescents Celexa is not approved for use in pediatric patients. (Se

Celexa is not approved for use in pediatic patients. (See Warnings and Precutions: Pediatric Use) Pooled analyses of short-term (4 to 16 weeks) placebo-controlled traits of antidepressand drugs (SSR)s and oth-ers) in children and adolescents with major depressive dis-order (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trails involving over 4000 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidat-ity) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%, No suicides occurred in these trails. NecroBOTION DESCRIPTION

DESCRIPTION Calcaradi (citalognam HB) is an orally administered selective seru-torin reuptake inhibitor (SSRI) with a chemical structure unrelated to that I of other SSRIs or di throycile, tetracycle, or other available andidepressant agents. Catalognam HB's is a reacerine bioyclic phthalane derivative designated (p)-1(3-dimethylaminopropy)-1-(4-furoopheny)-1,3-dinydrosobenozhuan-5-carbonitrile, HBr with the following structural formula:



The molecular formula is C20H22BrFN2O and its molecular weight s 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.

Celex (clauppearl injorticutione) is available is a slutter of a solution. Calexa in Hig in interringits equivalent (or in the containing Calexa in Hig in interringits equivalent to 10 mg clauppear base. Calexa 20 mg and 40 mg bables are linn-coated, or all, scored tables containing clauppear HB in interringits equivalent to 30 mg or 40 mg clauppear HB in interringits equivalent to 30 mg inactive ngrelients: copply/dome, com stardt, rorsszamellose dotum, giverein, Ladose monotyfelde, magnesium stearate, hyporemise, microorystalline cellulose, polyethylene gylod, and tables control of the condexa solution in the bege (10 mg) and prix (20 mg) tables. Celexa oral solution contains clauppar HBr equivalent to 2 mg/m, claupparts, purification, purified water, proylene gylod, methyl-migrefenists: solitol, purified water, proylene gylod, methyl-migrefenists: solitol, purified water, propriven gylod, methyl-

ingredients: sorbitol, purified water, propylene glycol, methyl-paraben, natural peppermint flavor, and propylparaben. CLINICAL PHARMACOLOGY

Pharmacodynamics The mechanism of action of citalopram HBr as an antidepressant The mechanism of action of clauopram Her as an antucepression is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). In vitro and in vivo studies in animals suggest that citalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norep-ingerhime (NE) and dopamire (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long-term (14-

to the inhibition of S-HT uptake is not induced by long-term (14-aly Instanter of task which calopane. Calopane is a racenic moture (SDS0), and the inhibition of S-HT reuptake by claiopram is primarily due to the (S)-enantioner. Claiopram has no or very low atfinity for S-HT r<sub>Ab</sub>. S-HT r<sub>Ab</sub>, dopamine D<sub>1</sub> and D<sub>2</sub>, ar<sub>1</sub>, ar<sub>2</sub>, and B-adrenergic, Instamine H<sub>1</sub>, amarn aminoturic and (GABA), muscanic cholnergic, and benzofizzapine receptors. A hardportism of muscanic, histamine cractic and the receptors and the mytopheteszet to be asso-ciated with various anticholinergic, setalative, and cardiovascular affects of their receptoring has benzofizzed.

# effects of other psychotropic drugs. Pharmacokinetics

The single- and multiple-dose pharmacokinetics of citalopram are The single daronampic back plantitudemined of backgrain the linear and does proportional in a lose range of 10-00 mg/day. Biotransformation of oitalogram is mainly hepate, with a mean ter-minal half-life of about 35 hours. With one daily doing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of citalo-prain 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 bioe quivalent.

quivalent. Absorption.and Distribution Following a single oral dose (40 mg tablet) of citalopram, peak bood fereis coccr at about 4 hours. The absolute bioavailability of citalopram was about 80% relative to an intravenus dose, and absorptions in at diffected by food. The volume of distribution of citalopram is about 12 LVg and the binding of citalopram (CT), demethy/citalopram (CC), and distentivipolatopram (DDCT) to human plasma proteins is about 80%.

human plasma proteins is about 60%. <u>Metabolism and Elimination</u> Following intravenous administrations of citalopram, the fraction of drug recovered in the unire as citalopram and DCT was about 10% and 5%, expectively. The systemic clearance of citalopram was 330 mL/min, with approximately 20% of that due to renal clearance. Citalopram is metabolized to demethylcitalopram (DCT),

Citalopram is metabolized to demethyloitalopram (DCT), diodemethyloitalopram (DDCT), diotopram-Hvoide, and a deami-nated propionic acid deividavie. In humans, unchanged olialopram is the predominant compound in plasma. Al steady state, the com-centrations of oblapinam's metabolites, DCT and DDCT, in plasma are approximately one-hall and one-terth, respectively, that of the parent rough, in vitro studies show that olialopram is at least 8 times more potent than its metabolites in the inhibition of servorim reutplack, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of relavoram

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the

cokinetics in subjects ≥ 60 years of age Age - Citalopram pharmacokinetics in subjects ≥ 60 years of age were compared to younger subjects in two normal volunteer stud-ies. 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

whereas in a multiple-does duty they were increased by 25% and 30%, respectively. 20 mg is the recommended does for most dicity planets (see **DOSAGE AND ADMINSTRATION**). Gender - In three pharmacokinetic studies (bital N=20), dible-pant AUC in woren was one and a half to two times that in men. This difference was not observed in five other pharmacokinetic studies (bital N=11). In clinical studies, no differences in steady state serum citalogram levels were seen between men (N=237) and women (N=38). Therew ere on gender differences in the pharmacokinetics of DCT and DDCT. No adjustment of dosage on the backet of endocrine transmission.

pharmacokinetics of DCT and DDCT in or 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 rec-ommended dose for most hepatically impaired patients (see DOSAGE AND ADMINISTRATION).

ulation Subgroups

DUSAGE AND ADMINISTRATION). The advanced of the Reduced real function – In patients with mild to moderate rerela function impainment, oral clearance of clalopram was reduced by 7% compared to normal subjects. Normal subjects Normal such patients is recommended. No information is evailable about the pharmacohortes of clalopram in patients with severely reduced renal function (creatinine clearance < 20 mL/min). Dunu-Dunu Inter-

Drug-Drug Interactions In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2E1, but did suggest that it is a weak inhibitor of CYP1A2, -2D6, and -2C19, Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism medi-ated by these cytochromes. However, *in vivo* data to address this

ated by these optiochromes. However, in wo data to address this guestion are limited by an efficient of the primary enzymes involved in the metabolism of oldatoma, it is expected that potent inhibitors of 344 (e.g., ketoconazole, inzonazole, and macroide antibitotics and optent inhibitors of CVP2CIP (e.g., omegrazole) might decrease the clearance of clalopram. However, coadministration of clalopram and the potent 344 inhibitor ketoconazole did not significantly allect the plasmackinetics of clalopram. Because clalopram is metabolized by multiple enzyme systems, inhibiton of a single enzyme may not appreciably decrease clalopram learance. Clalopram steady state levels were not sionificantly of a single enzyme may not appreciably decrease citalopmet clearance. Citalopma steady state levels were not significantly different in poor metabolizers and extensive 206 metabolizers after multiple-does administration of Celexa, suggesting that coadministration, with Celexa, of a drug that inhibits CVP2Do, is unlikely to have dividually significant effects on citalopman metab-olism. See **Drug Interactions** under **PRECAUTIONS** for more detailed information on available drug interaction data. **Clinical Efficacy Trials** 

The efficacy of Celeva as a treatment for depression was estab The efficacy of Celexa as a treatment for depression was setab-isated in two placebo-controlled studies (of 4 6 to weeks in dura-tion) in adul outpatients (ages 18-66) meeting DSMHI or DSMHIT criteria for major depression. Study 1 a 6 aveak trial in which patients received thed Celexa doses of 10, 20, 40, and 80 mg/day, showed that Celexa doses of 40 and 60 mg/day was effertive as measured by the Hamilton Depression Rahing Scale (HAMD) total score, the HAMD depressed mood item (item 1), the Montgomery Absect Depression Rahing 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 80 mg/day dose was not more effective than the 40 mg/day dose.

ou migroup does was not more elective riam me 40 migroup does, In study 2, a 4-week, placebo-controlled trial in depressed patients, of whom 85% met criteria for melancholia, the initial does was 20 mg/day, followed by titration to the maximum tolerated does or a maximum does of 80 mg/day. Patients treated with dose or a maximum dose of 80 mg/day. Patients treated with celeras showed significantly reaster improvement than placebo patients on the HAMD trad soure, HAMD item 1, and the CGI Severity score. In three additional placebo-controlled depression trials, the difference in response to treatment between patients rearing Celera and platient rearing placebo was not satisfi-cally 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-tem studies, depressed preliaties winh hard responded to Celera during an initial 6 or 8 weeks of acute treatment (tidee doses of 20 or 60 mg/day in one study, and flexible doses of 20-60 mg/day in the second study) were randomized to continuation of celera or to indexion. I hot this subsc. Celexa or to placebo. In both studies, patients receiving continued Celesa to jalacéba, Ihodh studies, palients receiving conflued Celesa teratimetra experiencia significantifi, lower relages rates over the subsequent 6 months compared to those receiving jalaceba. In the level close study, the deversal rate of depression relagee was similar in galents receiving 20 et 40 mg/day of Celesa, Analyses of the relationship between theraintent outcome and age, gender, and race did not suggest any differential exponsiveness on the basis of the patient characteristics. Comparison of Dimarial Threads Highly variable results have been seems in the datia development they have the results have been seems in the basis and evelopment

of all antidepressant drugs. Furthermore, in those circumstances when the drugs have not been studied in the same controlled clinwhen the drugs have not been studied in the same controlled off ical trial(s), comparisons among the results of studies evaluating the effectiveness of different antidispressant drug products are interently unreliable. Because conditions of testing (e.g., patient samples, investigators, doese of the treatments administered and compared, outcome measures, etc), yay among trials, it's vitu-ally impossible to distinguish a difference in drug effect from a di-ference due to one of the conformuling factors just enumerated. **NOCCATIONS AND USAGE** 

(a (citalonram HBr) is indicated for the treatment of depression The efficacy of Celeva in the treatment of depression was estab lished 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

of majo depressive disorder (see CLINICAL PHARMACDLOGY) h major depressive episode (DSM-W) implies a prominent and relatively persistert (nearly every day for at least 2 weeks) depressed or dysphotic mood that usual interferes with daily functioning, and includes at least five of the following nire symp-tions: depressed mod, loss of interest in usual activities, sginti-cant change in weight and/or appetite, insomia or hypersormal, spychmoridr agilation or relatration, increased failure, feelings of guild or worthlessness, solwed thinking or impaired concentra-ties a nuiside nature or aveided lobation. tion a suicide attemnt or suicidal ideation sant action of Celexa in hospitalized depressed The antidepres

ents has not been adequately studied.

patients has not been adequately studied. The efficacy of Cavain maintaining an antidepressant response for up to 24 weeks following to 16 weeks of acute treatment was demonstrated in two placeb-controller trials (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Cleans for example priority acuted periodically re-evaluate the longterm usefulness of the drug for the individual patient. CANTRAINIPOLICIES CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS). Concomitant use in patients taking pimozide is contraindicated (see **PRECAUTIONS**).

Celexa is contraindicated in patients with a hypersensitivity to citalogram or any of the inactive ingredients in Celexa.  $\ensuremath{\textbf{WARNINGS}}$ WARNINGS-Clinical Worsening and Suicide Risk

# Clinical Worsening and Suicide Risk Patients with major depressive disorder (MDD), both adult and

pediatric, may experience worsening of their depression and/or pediatir, may experience worsening of their depression and/or the emregnece of suicidal tediation and behavior (suicidality) or unusual changes in behavior, whether or no they are taking anti-depressant medications, and this risk may persist until significant emission occus. There has been a long-standing concern that antidepressants may have a role in inducing worsening di Sepre-sion and the emergence of suicidal timiting and behav-(or (suicidality) in sorti-tem studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric dis-orders.

orders. Pooled analyses of short-term placebo-controlled trials of 9 anti-Pooled analyses of short-error placebo-controlled trials of 8 anti-depressant durgs (SSR) and others) in olidieen and adulecents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suic-dality) during the first lew months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, hive the placebo risk of 2%. There was considerable viaritation in risk among drugs, but a ten-dency toward an increase for almost all drugs studied. The risk of antidefible transmission to execution the increase for almost all dency toward an increase for almost all drugs studied. The nsk of suicidality was most consistently observed in the MDD trials, but there were signals of risk anising from some trials in other psychi-atric indications (obsessive compulsive disorder and social anxietv disorder) as well. No suicides occurred in any of these tri-

ety disorder) as well. No suicides occurred in any of these thi-als. It is unknown whether the suicidary fixed readers back extends to longer-term use, i.e. beyond seveal months. It is alow unknown whether the suicidary fixed seturds to adults. All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsen ing, suicidarity, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or care-givers during the first 4 weeks of treatment, then at 12 weeks, and as givers during the tirst 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telphone may be appropriate between face-to-face visits. Adults with MDD or co-morbid depression in the setting of other psychiatic lines being treated with antidepressants should be observed similarly for clinical worsening and suici-ality, especially during the initial few months of a course of drug therapy, or a times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insom-nia, irritability, hostility, aggressiveness, impulsivity, akathisia (psy-chomotor restlessness), hypomania, and mania, have beer reported in adult and pediatric patients being treated with antide reported in adult and pediatric patients being treated with antide-pressnals for major depressive disordra as well as for other indi-cations, both psychiatric and nonpsychiatric. Although a causal link between the emergence of sub-stream synghoms and either the worsening of depression and/or the emergence of subidal impulses has not been established, there is concern that sub-synghoms may represent precursors to emerging subidally. Consideration should be given to changing the therapeutic regi-men, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing energent subidally or symptoms that might be precursors to worsening depression or subidally, especially if these symptoms are severe, aburt on eard or the not and refits pre-

are severe, abrupt in onset, or were not part of the patient's pre-

are severe, abrupt in orset, or were not part of the patient's pre-senting symptoms. If the decision has been made to discontinue treatment, medica-tion should be targened, as rapidly as it leasible, but with corpli-tion that abrupt discontinuation can be associated with certain symptoms (see PERCAUTIONS and DOSAGE AND ADMINIS-TRATION—Discontinuation of Treatment with Celexa, for a description of the risks of discontinuation of Celexa). Families and caregivers of pedicitric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence

alerted about the need to monitor patients for the emergence of agritation, intrahility, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Celexa should be written for the smallest quantity of tablets con-sistent with qode calent management, in order to reduce the risk of overdoose. Families and caregivers of adults being treated for prescent should be similary advanced. The family endocument of prescent should be similary advanced. The family channels con-tingences in the barries of adults being treated for

Screening Patients for Binglar Disorder: A major degressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that

generally believed (though not established in controlled thail) that treating such an ejecide with an antidepressant alone may increase the likelihood of preoplation of a mixedimanic episode in patients at risk to topland scored: Weither any of the symp-toms described above represent such a conversion is uniforwan. Powerer, prior to initialing treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk tor bipolar disorder, such screening should include a detailed psychiatric histopy, including a family history of sucide, bipolar disorder, and depression. It should be noted that Celexa is not approved for use in treating bipolar demression.

bipolar depression. Potential for Interaction with Monoamine Oxidase Inhibitors Potential for Interaction with Monoamic Oxidaes Inhibitors In patients receiving servionin regulate inhibitor (MAOL), there have been reports of servious, sometimes ratal, reactions including hyperthemia, rigidity, myoclorus, autoomic instability with possible rapid fluctualexisms of vital signs, and mental status changes that include extreme aglitation progressing to definum and coma. These reactions have also been reported in patients who have recently discontinued SSR treatment, and have been started on an MAOL some cases presented with features resembling neuroptic maingrant syndrome. Furthermore, lim-ited animal data on the effects of combined use of SSRIs and MoOls succest that these druces any act smersiticality to eleted ainma data on the effects or combined use of SSHs and MADIs suggest hat these drugs may act sprengsically to ele-vate blood pressure and evoke behavioral excitation. Therefore, its recommended that Celeva should not be used in combination with an MAOJ, or within 14 days of discontin-ing heatment with an MAOJ, and the strength and the strength end and the strength and the strength and the strength and below after stopping Celeva before starting an MAO. PRECAUTIONS

# Discontinuation of Treatment with Celexa During marketing of Celexa and other SSRIs and SNRIs (serotonin

and norepinephrine reuptake inhibitors), there have been sponta-neous reports of adverse events occurring upon discontinuation of

these drugs, particularly when abrupt, including the following: dys phoric mood, initiability, aptitation, dizziness, sensory disturbances (e.g., paresthesis such as electric brock sensations), antiely confusion, headache, lethargy, emotional lability, insorma, and hypomania. While these events are generally self-limiting, there have been reports of sensor discontinuation symptoms.

Patients should be monitored for these symptoms when discon Patents should be monitored to these symptoms when discon-tinuing heatment with Celexa. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If individually symptoms cour following a decrease in the dose or upon discontinuation of the attranet, then resuming the previously prescribed dose may be considered. Subsequentity, the rhysician may continue decreasing the dose but at a more gradual rate (see DOSARE aND ADMINISTRATION).

Celexa® ram hydrobr ets/Oral Solu

(citalopra Tablet:

Anormal Bleeding Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demon studies, both of the case-control and cohord design, have demon-strated an association between use of copychotopic drugs that interfere with seretonin resphale and the occurrence of upper gas-torinstelinal belong. In two studies, concurrent use of a non-teroidal arti-inflammatory drug (NSAID) or aspirin potentiated the risk of beering (see Drug Interactions). Although these studies tocused on upper gastrointestinal belong, there is to see helines that beering at other sites may be similarly potentiated Patients should be calculated regarding the risk of beering calculated the conculation. other drugs that affect coagulation

<u>Hyponatremia</u> 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 recov ered with discontinuation of Celexa and/or medical intervention Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major with other marketed drugs enecuve in the treatment of major depressive disorder. <u>Activation of ManialHypormania</u> In placebo-controlled trials of Celexa, some of which included

In placed-controlled traits of Celexa, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1053 patients treated with Celexa and in none of the 446 patients treated with placebo. Activation of mania/hypo-The the particle sector with pacetors. Advantation in the initial impor-menta has also been reported in a small proportion of patients with major affective disorders treated with other marketed antide-pressants. 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 Attriougn anticonvulsant effects of citalopram have been observe in animal studies, Celexa has not been systematically evaluated i patients with a seizure disorder. These patients were excluded froi official studies during the product's premarketing testing. In olinic trials of Celexa, seizures occurred in 0.3% of patients treated wit tiu hote 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

Calexa (a rate of one patient per 89 years of exposure) and 0.5% of patients treated with placob (a rate of one patient per 50 years of exposure). Like other antidepressants, Celexa should be intro-duced with care in patients with a history of escure disorder. Installers in more and Motor Performance in studies in more and works of the start of the studies of the patient with a history of escure disorder. Interference with Cognitive and Motor Performance installes in more and works of the start of the studies of the patient with a studies in more index of the start of the sta

not associated with the development of clinically significant ECG

In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of

decreased and plasma concentrations were increased. The use of clears in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (se DOSAGE AND ADMINISTRATION). Because clalopram is extensively metabolized, excretion of unchranged drug in unite is a minor oracle el elimination. Uniti ade-quate numbers of patients with severe real impairment have been erickland durig chronic treatment with Celsaa, however, it should be used with caution in such patients (see DOSAEE AND ADMINISTRATION)

Information for Patients Physicians are advised to discuss the following issues with

Physicians are advised to discuss the following issues with patients for whom they prescribe Celex. Although in controlled studies Celexa has not been shown to impair psychotomy performance, any psychotache drug may impair judgment, thinking, or motor skills, so patients should be cautored about pertaing hazardous a machines, including auto-mobiles, unit they are reasonably certain that Celexa therapy does not affect ther ability to reage an such advilles. Patients should be told that, atthough Celexa has not been shown to experiments with romal solicitos to increase the methal and the operations with romal solicitos to increase the methal and the solicitos.

notor 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 tak-

ing, or plan to take, any prescription or over-the-counter drugs, as

ing or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions. Patients should be cautioned about the concomitant use of cleara and NSANs, segrinr, or dref workings that after coogulaton since the combined use of psychotropic drugs that interface with serotorin reuptake and these agents has been associated with an increased risk of bleeding. Patients should be advised to notify their physician if they become gregariar or infand to become pregram during therapy. Patients should be advised to notify their physician if they are breastfeeding an infant.

preastfeeding an infant. While patients may notice improvement with Celexa therapy in 1 to 4 weeks, they should be advised to continue therapy as

U \* weets, line and a barrier of commercian and a single directed. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Celexa and should coursel them in the appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Celexa. The prescriber or health precisional should instruct patients, their families, and their caregivers to read the Medication Calide and should assist them in unvectanding its contents. Patients should be given the opportunity to discuss the contents

of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be advised of the following issues and asked to

alert their prescriber if these occur while taking Celexa. Clinical Worsening and Suicide Risk: Patients, their families,

Clinical Worsening and Suicide Risk: Patients, Their families, and their caregives should be encouraged to be alter to the emer-pence of anxety, aglation, panic attacks, insorma, initiality, tostility, aggression, and suicida disatinis (psychomotor res-lessness), hypomania, mania, other unusal damages in behavior, during antidepressant restanter and when the does a daulsed up ordown. Families and caregivers of patients should be achiesed to besieve for the emergence of such symptoms should be reported to the patient's presenter or health professional, sep-ality if the presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavpatient spesening symptoms such as these may associated with an increased risk for suicidal thinking and behav-ior and indicate a need for very close monitoring and possibly changes in the medication.

changes in the medication. Laborator Treat en o specific laboratory tests recommended. Drug Interactions CNS Drugs - Given the primary CNS effects of citalopram, caution Shouldb euced when it is taken in combination with other centrally acting drugs. Activid - Almough citalopram did not potentiate he cognitive and Activid - Jamough citalopram did not potentiate he cognitive and

motor effects of alcohol in a clinical trial, as with other psy-chotropic medications, the use of alcohol by depressed patients

taking Celexa is not recommended. Monoamine Oxidase Inhibitors (MAOIs) - See CONTRAINDICA-TIONS and WARNINGS.

TONS and WARNINGS. Drugs That Instrieve With Hemostasis (NSAIDs, Asprin, Warfarin, eL). Serotion relaxes by platelist plays an important role in hemostasis. Epidemiological studies of the case-control and obort design that we denostrated an association between use of syschotropic drugs that interfere with serotion recipitae and the occurrence of upper gastroinestinal beleding have also show that concurrent use of an NSAID or asprin potentiated the sky of bleding. Thus, patient's should be cauloned about the use of such drugs concurrently with Celexa.

of such drugs concurrently with Celexa. 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<sub>max</sub> 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 does of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

einer ciaopram or orgoxin. Lithium - Coadministration of Celexa (40 mn/dav for 10 davs) 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 levels should be inclined with appropriate adjustment of the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalo-pram, caution should be exercised when Celexa and lithium are

pram, caution should be excreased when Cleaka and Intimum are administered. Primozióe - In a controlled study, a single dose of primozióe 2 mg co-administered in dialogram 40 mg given once daily for 11 days was associated with a mean increase in OC values of appointante) // meas compared to primozióe given adore. Cleakhartismi of this phermacologinantic interacións in mutodom. Theophyline - Combined administration of Cleaka (40 mg/day for 21 days) and the CVP1A2 substrate theophyline (single dose 0 20 mg) did not faffer the harmaconvenients of theophyline. Theo 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was

effect of theophyline on the pharmacokinetics of ortatogram was not evaluated. Sumatriptan - There have been rare postmarketing reports describing patients with wakness, hyperreflexia, and incoordina-tion following the use of a SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluxcetine, fluxo-amine, parxostine, sertatiline, catalogram) is chincially warranted, appropriate observation of the natient 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

Profitrombin time was increased by 3%, the united symmetry of which is unknown. Carbamazepine - Combined administration of Celera (40 mg/day for 14 days) and carbamazepine (thated to 400 mg/day for 35 days) did not significantly affect the pharmacoknetics of carba-mazepine, a CPPA4 substate. Although trough clabpram plasma levels were unaffected, given the enzyme-inducing prop-relies of carbamazene, he possibility that carbamazene might increases the clearance of clabpram should be considered if the time Arease are acadiministered.

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 pharmacoki

gle dise of 0.25 mg) did not significantly affect the pharmacoin-metics of either claptam or triazolan. Ketoconazole - Combined administration of Celeva (40 mg) and ketoconazole (20 mg) decreased the C<sub>mat</sub> and AUC of keto-conazole by 21% and 10%, respectively, and did not significantly affect the pharmacointellis of claicopam. CYP344 and 2C19 are the primary enzymes indicated that CYP344 and 2C19 are the primary enzymes indicated that CYP344 and 2C19 are the primary enzymes involved in the reliabolism of clabiopam. However, administration of clabio-pam (40 mg) and ketoconazole (200 mg), a potent inhibitor of clalopram. Because citalopram is metabolized by multiple enzyme systems, hibition of asingle enzyme may not acoreciaenzyme systems, inhibition of a single enzyme may not apprecia

erzyme systems, inhibition of a single erzyme may not apprecia-by decrease cladgram dearance. Metoprotol - Administration of 40 mg/day Celexa for 22 days resulted in a two-fold increase in the Jasma levels of the beta-adrenergb blocker metoprotol. Increased metoprotol plasma levels els have been associated with decreased cardioselectivity. Coadministration of Celexa and metoprotol had no clinically sig-nificant effects on blood pressure or heart rate. Impramine and Other Tiroyclie Artibiogressants (TCAs) - (n vitro

Impraning and Other Processants (TORS) - In view studies suggest that citalopram is a relatively weak inhibitor or CYP2DB. Coadministration of Celexa (40 mg/day for 10 days) with the TCA impramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of CYP2/bit, and not significatify after the plasma concentrations of impramme or classification. However, the concentration of the impramme metabolite designamine was increased by apport-able 50%. The clinical significance of the designamine change is unknown. Nevertheless, caution is indicated in the coadminu-tation of TCAs with Celexa. Electrocomulsive Therapy (ECT) – Three are no clinical studies of the combined use of electrocomvisive therapy (ECT) and Celexa.

the combined use of electroconvulsive therapy (ECT) and Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis Citalopram was a opram was administered in the diet to NMRI/BOM strain mice

## Medication Guide

# About Using Antidepressants in Children and Teenagers What is the most important information I should know if my child is being prescribed an antidepressant?

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

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

Children and teenagers sometimes think about suicide, and

Antidepressants increase suicidal thoughts and actions in

some children and teenagers. But suicidal thoughts and

actions can also be caused by depression, a serious med-

ical condition that is commonly treated with antidepres-

sants. Thinking about killing yourself or trying to kill your-

A large study combined the results of 24 different studies

of children and teenagers with depression or other ill-

nesses. In these studies, patients took either a placebo

(sugar pill) or an antidepressant for 1 to 4 months. No one

committed suicide in these studies, but some patients

became suicidal. On sugar pills, 2 out of every 100 became

suicidal. On the antidepressants, 4 out of every 100

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients

Bipolar illness (sometimes called manic-depressive

If any of these are present, make sure you tell your health-

To try to prevent suicidal thoughts and actions in your

child, pay close attention to changes in her or his moods

or actions, especially if the changes occur suddenly. Other

important people in your child's life can help by paying

attention as well (e.g., your child, brothers and sisters,

teachers, and other important people). The changes to look

Whenever an antidepressant is started or its dose is

After starting an antidepressant, your child should gener-

· After 12 weeks, follow your healthcare provider's advice

 More often if problems or questions arise (see Section 3) You should call your child's healthcare provider between

out for are listed in Section 3, on what to watch for.

changed, pay close attention to your child.

ally see his or her healthcare provider: • Once a week for the first 4 weeks

• Every 2 weeks for the next 4 weeks

about how often to come back

visits if needed.

After taking the antidepressant for 12 weeks

care provider before your child takes an antidepressant. 2. How to Try to Prevent Suicidal Thoughts and Actions

A personal or family history of attempting suicide

### 1. There is a Risk of Suicidal Thoughts or Actions

many report trying to kill themselves.

self is called *suicidality* or *being suicidal*.

patients became suicidal.

A family history of bipolar illness

with

illness)

Celexa® (citalopram hydrobromid Tablets/Oral Solution Celexa® ram hydrobr ets/Oral Solu (citalopra Tablets

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

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

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

Other unusual changes in behavior or mood

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

Stopping an antidepressant suddenly can cause other symptoms.

### 4. There are Benefits and Risks When Using Antidepressants

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

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

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

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

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

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

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

\* Prozac® is a registered trademark of Eli Lillv and Company

\*Zoloft® is a registered trademark of Pfizer Pharmaceuticals

\* Anafranil® is a registered trademark of Mallinckrodt Inc.

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

and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for caranogenicity of citalogram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended human daily dose (MRHD) of 0 mg on a surface area (mg/m<sup>2</sup>) basis. There was an increased inoldner of small intestine caronom an rate receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, dose which are approximately 1.3 and 4 times the MRHD. respectively, on a mg/m<sup>2</sup> basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is

<u>Mutagenessis</u> (Catalopram was mutagenic in the *in vitro* bacterial reverse muta-tion assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic adviation. It was clas-togenic in the *in vitro* Chinese hametric lung cell assay for chro-mosorial aberrations in the presence and absence of metabolic adviation. Catalopram was not mutagenic in the *in vitro* ornam-malian forward gene mutation assay (HPPT) in muse lymphome efforts are acquired in utrificial in uterbold left. DMI methodic Mutagenesis Citalopram v cells or in a coupled in vitro/in vivo unscheduled DNA synthesis Cells of in a coupled in without word inscribedued DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chro-mosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Induse inductional satesys. Impairment of Zeriality When citalopram was admissible transite rank prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at al doses, and fertility was decreased at doses - 32 mg/kg/day, approxi-mately 5 times the MRHD of 60 mg/day on a body surface area (mg/m<sup>2</sup>) basis. Getation duration was increased at 48 mg/kg/day, approximately 6 times the MRHD.

### Pregnancy

Pregnancy Category C In animal reproduction studies, citalopram has been shown to In amma reproduction studies, citatopram has been shown to have adverse effects on embryoffetal and postnatal development, including teratogenic effects, when administered at doses greater than human theraneutic dose.

nan human therapeutic doses. 1 two rat embryoftetal development studies, oral administration of italopram (32, 56, or 112 mg/kg/day) to pregnant animals during ne period of organogenesis resulted in decreased embryoftetal with and survival and an increased incidence of fetal about growth and survival and an increased including or rotal dense malities (including cardiovascular and skeletal defects) at the hig dose, which is approximately 18 times the MRHD of 60 mg/day o s) at the high dose, which is approximately 18 times the MHH of 60 m (dg4) on a body surface area (mm)<sup>2</sup> has in: this does was also associ-ated with maternal toxicity (clinical signs, decreased body weight gain). The developmental, no-effect dose of 56 mgk(dg4) is approximately 9 times the MHH Do a mg/hc basis. In a tabit study, no adverse effects on embryofetal development were boserved at doses of up to 16 mgk(dg4), or approximately 5 times the MHHD on a mg/hc basis. Thus, teratogenie effects were observed at doses up to 16 mgk(dg4), or approximately 5 times the MHHD on a mg/hc basis. Thus, teratogenie effects were observed at in the atternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with citalonram (4.8, 12.8, o 32 mg/kg/day) from late gestation through weaning, increased off spring mortality during the first 4 days after birth and persistent off spring mortally during the first 4 days after bith and presistent off-spring growth relations were observed at the highest dose, which is approximably 5 times the MRHO on a mymic basis. The noellest dose of 12 a myojculys is approximately 2 times the MRHO on a mg/m<sup>2</sup> basis. Similar effects on offspring mortality and growth were seen when dans were itselied throughout gesation and early factions at doses 2 4 myojculys, approximately 4 times the MRHO on a mg/m<sup>2</sup> basis. A noeffect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant woment, therefore, cladoparan should be used during pregnancy only if the potential benefit justifies the potential risk to the felus. Neonates exposed to Celeva and other SSRIs or SNRIs, late in the third timester, have developed complications requiring pro-

Neonates exposed to Celeva and other SSRIs or SNRIs, tate in the third timester, have developed complications requiring pro-longed hospitalization, respiratory support, and tube feeding, south complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, acourts, surveits, exercutes, temperature instability, leading diffi-oulty, vomiting, hypodynemia, hypotonia, hypertonia, hyper-rellexia, terrori, jitteriness, imitability, and constant crying. These teuruss are constant with either a direct toxic effect of SSRis reatures are consistent with entire a direct toxic enect or Sama and SNRIs or, possibly, a drug discontinuation syndrome. I should be noted that, in some cases, the clinical picture is consis tent with serotonin syndrome (see **WARNINGS**). When treating a pregnant woman with Celexa during the third

trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINIS-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 excreted in numan oreast milk. There have been two reports infants experiencing excessive somnolence, decreased feed and weight loss in association with breastleeding from a cit pram-treated mother; in one case, the infant was reported pran-treated mother; in one case, the infant was reported recover completely upon discontinuation of citalopram by mother and in the second case, no follow-up information v available. The decision whether to continue or discontinue etil nursing or Celexa therapy should take into account the risks citalopram exposure for the infant and the benefits of Celexa tre may bot in mother.

Mention and moment. Pediatric Use Safety and effectiveness in the pediatric population have not b established (see BOX WARNING and WARNINGS—Clin

Worsening and Suicide Risk). Two placebo-controlled trials in pediatric patients with MDD have been conducted with Cele and the data were not sufficient to support a claim for use in p atric patients. Anyone considering the use of Celexa in a child adolescent must balance the potential risks with the clinical ne Geriatric Use Of 4422 patients in clinical studies of Celexa, 1357 were 60 a over, 1034 were 65 and over, and 457 were 75 and over. No ov all differences in safety or effectiveness were observed betwe these subjects and yourger subjects, and other reported diri-experience has not identified differences in responses betwe the dekey and yourger patients, bud greater sensitivity of so older individuals cannot be ruled out. Most alderly patients treat

with Celexa in clinical trials received daily doses 40 mg (see DOSAGE AND ADMINISTRATION) s between 20 In yoos userve and Aumittis I HAITION).
 In two pharmacokinetic studies, citalopram AUC was increased 23% and 30%, respectively, in eldenly subjects as compared younger subjects, and its half-life was increased by 30% and 50 respectively (see CLINICAL PHARMACOLOGY).
 20 mg/day is the renormanded does have and statistical

20 mg/day is the recommended dose for most elderly patie (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS The premarketing development program for Celexa inclu citalopram exposures in patients and/or normal subjects from different groups of studies: 429 normal subjects in clinical pl macology/pharmacokinetic studies: 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient-exposure years. There were, in addi-tion, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Celeax varied greatly and included (in overlapping call-price) open-label and double-bint bidliss, inpatient and outpa-tient studies, fixed-dose and dose-thration studies, and short-term of lonobram exposure. A dhose a varies wat short-term of lonobram exposure. A dhose a varies of the owner and lonobram exposure. A dhose a varies wat short-term of lonobram exposure. A dhose a varies of the owner and lonobram exposure. A dhose a varies of the owner and lonobram exposure. A dhose a varies of the owner assess of the owner and the owner and the owner assess of the owner assess of the owner and terms. and long-term exposure. Adverse reactions were assessed by col-lecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of oph-

in organization methods, and one of the second of the s meaningue estimate on the propriority 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) ucuasors hart tolow, standard Wold Health Organization (WHO) terminologi has been usef to disatly profied sitvere events. The stated frequencies of abverse events represent the propri-tion of individual who experiences (a lass) none, at textemet-energient adverse event of the type listed. An event was consid-ered traditionation of the type listed, and event was consid-ered withe consist pricety following adeline evaluation. Adverse Findings Deserved in Short-Term, Placebo-Controlled This

Adverse Events Associated with Discontinuation of Treatment Among 1063 depressed patients who received Celexa at dos 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 al 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 one in this table. TABLE 1

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled, Depressio Trials Per

1 0100	Due to Adverse Event	
	Citalopram (N=1063)	Placebo (N=446)
Body System/Adverse Event	(,	
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomitina	1%	0%
Central and Peripheral		
Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Agitation 1% of 2% of 2% of 2% of 2% of 2% of 2% of 1% of 2% patients treated with Celexa and for which the incidence in patients treated with Celexa was greater than the incidence in

patients retaided with Celexa was greater than the incidence in placebo-retaid patients. The prescriber should be aware that these figures cannot be used to predict the incidence of advarse events in the course of usual medical practice where patient characteristics and other factors differ tom those which prevaled in the enicital trials. Similarly, the cled frequencies cannot be compared with figures obtained from other clinical investigators involving offlerent treatments, uses, and investigators. The clied figures, however, do provide the pre-scribing physician with some basis for estimating the relative con-tribution of drug and non-dug factors to the adverse event inci-dence rate in the roundation stuffert. dence 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:

m is ts of	(Percentage of Patients Reporting Event)					
ding,	Body System/Adverse Event	Celexa	Placebo	of Celex Followin		
talo-	body oystella Autorse Etern	N=1063)	(N=446)	adverse		
d to	Autonomic Nervous System		(	REACTI		
/ its	Disorders			multiple		
was	Dry Mouth	20%	14%	a trial v		
ither	Sweating Increased	11%	9%	reported		
is of	Central & Peripheral Nervous			2 or else		
reat-	System Disorders			was rem		
	Tremor	8%	6%	uninform		
	Gastrointestinal Disorders			tant to er		
been	Nausea	21%	14%	ing treat		
nical	Diarrhea	8%	5%	Events a		
407	Dyspepsia	5%	4%	of decre		
exa.	Vomiting	4%	3%	quent ac		
oedi-	Abdominal Pain	3%	2%	sions in		
ld or	General			those or		
eed.	Fatigue	5%	3%	patients;		
	Fever	2%	<1%	patients.		
and	Musculoskeletal System			Cardiov		
wer-	Disorders			hypoten		
/een	Arthralgia	2%	1%	(extremit		
nical	Myalgia	2%	1%	ing, myo		
/een	Psychiatric Disorders			ischemia		
ome	Somnolence	18%	10%	tion, can		
ated	Insomnia	15%	14%	Central		
and	Anxiety	4%	3%	paresthe		
	Anorexia	4%	2%	nia, extra		
d by	Agitation	3%	1%	tractions		
d to	Dysmenorrhea <sup>1</sup>	3%	2%	thesia, a		
50%,	Libido Decreased	2%	<1%	sis, stup		
	Yawning	2%	<1%	Endocri		
ents	Respiratory System Disorders			mastia.		
	Upper Respiratory Tract Infection	5%	4%	Gastroir		
	Rhinitis	5%	3%	lence. Ir		
papr	Sinusitis	3%	<1%	hemorrh		
im 3	Urogenital			Rare: co		
har-	Ejaculation Disorder <sup>2,3</sup>	6%	1%	ulcer, ga		
ents	Impotence <sup>3</sup>	3%	<1%	rectal he		

\*Events reported by at least 2% of patients treated with Celexa are reported, except for the following events which had an inci-dence on placebo 2 Celexa: headache, asthenia, dizziness, con-stipation, palpitation, vision abnormal, sleep disorder, nervousigitis, micturition disorder, back pain. tor used was for females only (N=638 Celexa; N=252 vnaitis, mict

Placebo).
 Primarily ejaculatory delay.
 Denominator used was for males only (N=425 Celexa; N=194

### placebo).

placebo). <u>Dose Dependency of Adverse Events</u> The potential relationship between the dose of Celexa adminis-tered 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 Celexa 10, 20, 40, and 60 mg. Jonckneeres вели вы теченее о positive dose response (p<0.05) for the following adverse events: tatigue, impotence, insomnia, sweating increased, somnolence

Male and Female Sexual Dysfunction with SSRIs

Male and Fenale Sexual Dystruction with SSRIs a Athrough changes in sexual desire, sexual performance, and sex-ual satisfaction often occur as manifestations of a psychiatric dis-ment. In particular, some evidence suggests that SSRIs can cause such untoward sexual apoptiences. Relateba estimates of the inodence and sevenly of untoward experiences involving sexual desire, performance, and satisfac-tion are afficult to obtain, however, in part because petients and physicians may be reluctant to discuss them. Accordingly, esti-mates of the inodence of untoward sexual experience and petro-mance oted in product labeling, are likely to underestimate their actual inodence. actual incidence.

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. Colova Discolu

and	nearnen	(425 males)	(194 males)
	Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
na	Libido Decreased	3.8% (males only)	<1% (males only)
ibo	Impotence	2.8% (males only)	<1% (males only)

n female depressed patients receiving Celexa, the reported inc

In female depressed patients receiving Celexa, the reported inci-dence of decreased libitio and anragsamia was 1.3% (n-638 females) and 1.1% (n-622 females), respectively. There are no adequately designed studies examining sexual dys-function with clustoran treatment. Priapism has been reported with all SSRs. When it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRs, physicians should noutinely inguire about such possible side effects. <u>Vial Sign Changes</u> Celexa and pleatebo groups were compared with respect to (1) mean change from baseline in vial signs (pulse, systolic blood patients meeting citeties to potentially clinically significant changes un clinically important changes in vial signs associated with Celeva and clinically important changes in vial signs associated with Celeva 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.

Verexa reaument 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) Cleara and paceou groups were compared win respect of (1) mean change from baseline in various serum chemistry, hematol-ogy, 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 Celera treatment

Celea teamment. EGG Changes Electrocardiograms from Celexa (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various EGG parameters, and (2) the incidence of patients meeting orients for potentially clinically significant changes from baseline in these variables. The only stabilisation incident dinuclication difference hosened was a decrease in 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 (citalooram HBr)

leva (citalopram HEP) arise is a list of WHO terms that reflect treatment-emergent se events, as defined in the introduction to the ADVERSE TIONS section, reported by patients treated with Celexa at le doese in a mage of 10 b 80 mg/day during any phase of within the premarketing database of 420 patients. All led events are included except those already listed in Table the time these methods for which a drun raises el events aré includel éxopt these already lieted in Table isentre in labeling. Tosse events for which a drug cause emote, those event terms which were so general as to be mative, and hose occurring in only one patient. It is impor-emphasize that, allowigh the events protect occurred dou-atiment with Cleiaxa, they were not necessarily caused by it, as a further categorized by doily system and listed in order averse in which so coursing on one or more occu-in al east 1/100 patients; interquent adverse events are coursen in loss them 1100 necleiot the tal east 1/100 DOSAGE AND ADMINISTRATION Initial Teamment Caleas (citalopram HB) should be administered at a initial dose of 20 mg or de day, generally with an increase to a dose of 40 mg dirburs of no less than one week. Altowich, extrain patients may require a dose of 60 mg/day, the only sludy pertinent to dose response for effectiveness of not demonstrate an advan-tage for the 60 mg/day dose over the 40 mg/day dose; dose above 40 mg are therefore not of dirandiry recommended. Celexa should be administered once daily, in the morning or evening, with or 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 mot-patients with severe renal impairment. Pertaint end by a colling and the californian the patients with severe renal impairment. Tertament of Pergoand Vomen During the Third Trimester Neonates exposed to Celexa and other SSNIs, late in the third timeser, have develoced complications erguing partients. incurring in less than 1/100 patients, innequent adverse events are incurring in less than 1/100 patients but at least 1/1000 s; rare events are those occurring in fewer than 1/1000

vascular - Frequent: tachycardia, postural hypotension, sion. Infrequent: hypertension, bradycardia, edema ties), angina pectoris, extrasystoles, cardiac failure, flushocardial infarction, cerebrovascular accident, myocardial a. Rare: transient ischemic attack, phlebitis, atrial fibrila-rdiac arrest hundle branch block

Irdiac arrest, bundle branch block. II and Peripheral Nervous System Disorders - Frequent: besia, migraine. Infrequent: hyperkinesia, vertigo, hyperto-trapyramidal disorder, leg cramps, involuntary muscle con-tapixa. Pare: abnormal coordination, hyperesthesia, pto-taxia. Area: abnormal coordination, hyperesthesia, pto-

rine Disorders - Rare; hypothyroidism, goiter, gyneco-

intestinal Disorders - Frequent: saliva increased, flatu-

Gasculiniesimi Disorder 5 - Frequent: same introsecu, incurso, Hence, Infeguent, gasting, gastroentenis, somatilis, enclation, hemorthoids, dysphagia, leeth grinding, grigvitis, esophagitis. Rare collis, gastric uec, cholekystis, cholelinitasis, duodenal uicer, gastroesophageal reflux, glossitis, jaundice, diverticultis, ret collis, gastric ucopis.

General - Infrequent: hot flushes, rigors, alcohol intolerance, syn-

cope, influenza-like symptoms. Rare: hayfever. Hemic and Lymphatic Disorders - Infrequent; purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. Rare: pul-monary embolism, granulocytogenia, lymphopenia, lymphope-nia, 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 glu-cose tolerance. Rare: bilirubinemia, hypokalemia, obesity, hypo-

cose bierance. Rate: billinthiemia, hypokalemia, obesty, hypo-dycemia, hepatik, dehyrdation. Musculoskeletal gystem Disorders - Infrequent: arthritis, mas-de vasienses skeletal pain. Rate: turbitis, desponsois. Psychiatric Disorders - Frequent: impaind concentration, amme-sia, apathy, depression, noreased appetite, aggravated depres-sion, saicide attempt, contaison. Infrequent: increased libito, aggressive reaction, paramia, drug dependence, depresonita-tion, halluoration, explorial, abitolic depression, delaison, paramoid reaction, emotional lability, pario reaction, psychosis. Are: catatonic reaction, melanothal weeks tolowing 6 of a weeks of initial relatificit (22 weeks tola), inone study, palenti were assigned randomly to placebor of the same dose of Celexa (20-40 mg/dsr) during maintenance freat-emnt as they had received during the acute stabilization phase, while in the other study, patients were assigned randomly to con-tinuation of Celexa 20 of 40 mg/dsr oy patecho, for maintenance treatment. In the latter study, the rates of relapse to depression were similar for the vol dose groups (see Clinical Thais under CLINICAL PHARMACQLORY). Based on these limited data, it is not arraw unberte the dose, of discharme saved to maintenance is not known whether the dose of citalogram needed to maintain euthymia is identical to the dose needed to induce remission. If adverse reactions are bothersome, a decrease in dose to 20 Reproductive Disorders/Female\* - Frequent: amenorhea. Infrequent: galactorhea, breast pain, breast enlargement, vaginal

advetse reactions are conditersome, a declease in dobe to zo mojfay can be considered. Discontinuation of Treatment with Celexa Symptoma associated with discontinuation of Celexa and other SSRs and SNRIs have been reported (see PRECAUTIONS). Patients should be monitored for these symptome when discon-tinuing treatment. A gradual reduction in the dose rather than Not send on female subjects only: 2955 Respiratory System Disorders - Frequent coughing Infrequent bronchitis, dysprea, pneumonia. Rare: asthma, laryngilis, bron-chospasm, pneumonilis, syutum increased.

arrhythmia, torsades de pointes, and withdrawal syndrome. DRUG ABUSE AND DEPENDENCE

DRUG ABUSE AND DEPENDENCE Controlled Subtance Class Celexa (cilappram HB) is not a controlled subtance. Physical and Psychological Dependence Anmal studies suggest that the atuse liability of Celexa is low. Celexa has not been systematically studied in humans for fits potential for abuse, bierance, or physical dependence. The pre-marketing clinical experience with Celexa did not reveal any vitig-seking behavior. However, these devariations were not system-atic and it is not possible to predict, on the basis of this limited remarketing the total with Celexa total with the mis-

alic and it is not possible to predict, on the basis of this limited experience, the evident to which a CM-Sactive drug will be mis-used, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Celeza patients for history of drug abuse and follow such patients closely, observing them for sign of misse or abuse (e.g., development of tolerance, incre-mentations of dose, drug seeking behavior).

OVERDOSAGE Human Experience In clinical trials of citalopram, there were reports of citalopram

In clinical initia of clauppartin, there were reports of clauppartin overdose, including overdoses of up to 2000 mg, with no associ-ated fatalities. During the postmarketing evaluation of citalopram, Celexa overdoses, including overdoses of up to 6000 mg, have been reported. As with other SSPIs, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely

reported. Symptoms most often accompanying citaloptem overdose, alone, or in combination with other drugs and/or alcohol, included dizi-ness, swalling, nausea, vomiling, temor, somolience, and sinu tarbycardia. In more rare cases, observed symptoms included annesia, confusion, coma, convulsions, hyperventilation, organosis, intabdomylosis, and ECG changes (including OT pro-longation, nodal rhythm, vertincular arrhythmia, and one possible neas of Instrates to onities).

Management of Overdose Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastic evacuation by larage and use of adi-vated darcard should be considered. Careful obsenation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large vol-me of distribution of calaporal, more diversis, dailysis, hemop-erlision, and exchange transitision are unlikely to be of benefit. There are no specific antidotes for Celeza. In unligh-drug in managing overdosage, consider the possibility of unligh-drug providement. The thysician should consider contactive rapids control center for additional information on the treatment of any overdose.

the third trimester, have developed complications requiring pro

longed hospitalization, respiratory support, and tube feeding (see

case of torsades de pointes). Management of Overdose

DOSAGE AND ADMINISTRATION

criospasin, preumonis, spoulin increased.
Skin and Appendages Disorders - Frequent: rash, pruritus.
Infrequent: photosensitivity reaction, urticana, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. Pare: arbung realment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolera-ble symptoms occur following a decrease in the dose or upon dis-continuation of treatment, then resuming the previously pre-scribed dose may be considered. Subsequently, the physician hvoertrichosis, decreased sweating, melanosis, keratitis, cellulitis, may continue decreasing the dose but at a more gradual rate. Switching Patients To or From a Monoamine Oxidase

puritus anic. Journal of the second s Ioss. Urinary System Disorders - Frequent: polyuria. Infrequent: mic-turition frequency, urinary incontinence, urinary retention, dysuria. Rare: facial edema, hematuria, oliguria, pyelonephritis, renal cal-

# 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 an MAOI (see CONTRAINDICATIONS and WARNINGS). (see CONTRAINUI HOW SUPPLIED

PRECAUTIONS). When treating pregnant women with Cele

Precover lows), when treamy pregnant women with Celead during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Celexa in the third trimester.

It is generally agreed that acute episodes of depression require In is generally agreed una acute cybooles or opposition 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 tota); here show the opposition de section acute of the term of the section of the

Maintenance Treatment

Other Events Observed During the Postmarketing Evaluation 
 Tables:
 NDC # 0456-4010-01

 Beige, oval, film-coated.
 Imprint on one side with "FP". Imprint on the other side with "10
 of Celexa (citalopram HBr) It is estimated that over 30 million patients have been treated with It is estimated frait over 30 million patients have been treated with celevas ance market introduction. Although no causal relationship to Celexa treatment has been found, the following adverse events have been popted to be temporally associated with Celexa treat-ment, and have not been described elsewhere in labeling acute renal failure, adahtisia, allergic reaction, anaphylaxis, angioedema, choreachetosis, chest pain, delirum, dysknesia, ecolymosis, geidema lencoviss, entymen multitome, gastroin-testraia hemorrhage, grand nal convulsions, hemolytic anemia, hepatic necrosis, mychoclum, anueutopite mailignant syndrome, nystagmus, pancreatilis, pragism, prolactinemia, profrombio cereased, IT pronoged, habdomydysis, servotni syndrome, spontaneous abortion, thrombocytopena, thrombosis, ventricular mythymine, torsade de pointes, and withdrawal syndrome.

 Impair of the side with PT
 Impair of the utile side with PC

 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

. int on the non-scored side with "20 mg". na Bottle of 100 NDC # 0456-4040-01

 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

Imprint on the non-scored side with "40 mg". Oral Solution:

# Ural 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

Stole at 25 (1/P) excursions permitted to 15 - 30°C (b4-66 F). AttiNAL TOXICOLOGY Retinal Changes in Rats Pathologic changes (degenerationlatrophy) were observed in the retinas of abino rats in the 2-year carcinogenicity study with table-pathologic changes (degenerationlatrophy) were observed in the retinal pathology in both male and female rats receiving 80 mg/sdg41 (31 miss the maximum ecommendid daily human dose of 60 mg on a mg/m<sup>2</sup> basis). Similar findings were not pre-sent in rats receiving 24 mg/sdg49 (virto years, in mice treated for 16 months at doses up to 240 mg/sdg44 (2, 20, and 10 times, respective), the maximum recommended daily human dose on a mg/m<sup>2</sup> 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.

plasma levels of CT, DCT, and DDCT similar to those observed in dogs at doses of a mg/cgtay. A subsequent intravenous dosing study demonstrated that in beagle dogs, DDCT caused OT po-longation, a known inis kladr for the desvered outcome in dogs. This effect occurred in dogs at doses producing peak DDCT plasma levels of 100 x320 nl (4)35755 times the man steady state DDCT plasma level measured at the maximum recom-mended human daily dose of 80 mg), hodos, peak DDCT plasma concentrations, whereas in humans, states bdcT plasma com-centrations, whereas in humans, states bdcT plasma com-centrations, averages 10 DDCT plasma comcentrations in 2020 otabi-pram-tratect individuals demonstrated that DDCT levels arely seceeded 70 nkt the hinghest measured level of DDCT human. exceeded 70 nM; the highest measured level of DDCT in human overdose was 138 nM. While DDCT is ordinarily present in brendoe was not minimie. When both is during the present in humans at lower levels than in dogs, it is unknown whether three are individuals who may achieve higher DDCT levels. The possi-bility that DCT, a principal metabolite in humans, may prolong the QT interval in dogs has not been directly examined because DCT is rapidly converted to DDCT in that species.

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