

SENTRALOPRAM AM-10 - citalopram hydrobromide, choline
Physician Therapeutics LLC

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Sentralopram AM-10

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of citalopram tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Citalopram is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

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



The molecular formula is C₂₀H₂₂BrFN₂O and its molecular weight is 405.35.

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

Citalopram hydrobromide is available as tablets.

Citalopram 10 mg tablets are biconvex, round shaped film coated tablets in strengths equivalent to 10 mg citalopram base. Citalopram 20 mg and 40 mg tablets are scored biconvex capsule shaped film coated tablets containing citalopram hydrobromide in strengths equivalent to 20 mg or 40 mg citalopram base. The tablets also contain the following inactive ingredients: copovidone, corn starch, croscarmellose sodium, lactose monohydrate, magnesium stearate, hypromellose, microcrystalline cellulose, polyethylene glycol, and titanium dioxide. Iron oxides are used as coloring agents in the peach (10 mg) and light pink (20 mg) tablets.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of citalopram hydrobromide as an antidepressant 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 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 D₁ and D₂, α ₁-, α ₂-, and β -adrenergic, histamine H₁, 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.

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 less than 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 CYP1A2, -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 citalopram tablets, suggesting that coadministration, with citalopram tablets, 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 citalopram tablets 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 citalopram tablets doses of 10, 20, 40, and 60 mg/day, showed that citalopram tablets 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 citalopram tablets 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 citalopram tablets 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 citalopram tablets 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 citalopram tablets or to placebo. In both studies, patients receiving continued citalopram tablets 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 citalopram tablets.

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

Citalopram tablets are indicated for the treatment of depression.

The efficacy of citalopram tablets 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 citalopram tablets in hospitalized depressed patients has not been adequately studied.

The efficacy of citalopram tablets 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 citalopram tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Citalopram tablets are contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in citalopram tablets.

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the best predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

TABLE 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
less than 18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
greater than or equal to 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with Citalopram Tablets, for a description of the risks of discontinuation of citalopram tablets).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, 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 citalopram should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed

(though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that citalopram is not approved for use in treating bipolar depression.

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that citalopram tablets should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping citalopram tablets before starting an MAOI.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including citalopram treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of citalopram with MAOIs intended to treat depression is contraindicated. If concomitant treatment of citalopram with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of citalopram with serotonin precursors (such as tryptophan) is not recommended. Treatment with citalopram and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

PRECAUTIONS

General

Discontinuation of Treatment with Citalopram Tablets

During marketing of citalopram and other SSRIs and SNRIs (serotonin and norepinephrine reuptake

inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with citalopram. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding

SSRIs and SNRIs, including citalopram, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of citalopram and NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including citalopram. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when citalopram was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see Geriatric Use). Discontinuation of citalopram should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Activation of Mania/Hypomania

In placebo-controlled trials of citalopram tablets, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with citalopram tablets 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, citalopram tablets should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of citalopram have been observed in animal studies, citalopram tablets have 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 citalopram tablets,

seizures occurred in 0.3% of patients treated with citalopram tablets (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, citalopram tablets should be introduced with care in patients with a history of seizure disorder.

Interference with Cognitive and Motor Performance

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

Use in Patients with Concomitant Illness

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

Citalopram tablets have 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 citalopram tablets in clinical trials were evaluated and the data indicate that citalopram tablets are 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 citalopram tablets 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 citalopram tablets, however, they 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 citalopram tablets.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of citalopram and triptans, tramadol or other serotonergic agents.

Although in controlled studies citalopram tablets have not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking, or motor skills, so patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that citalopram tablets therapy does not affect their ability to engage in such activities.

Patients should be told that, although citalopram tablets have not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of citalopram tablets 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 cautioned about the concomitant use of citalopram and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

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

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

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

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with citalopram and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is available for citalopram. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide 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 citalopram.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs including citalopram, and the potential for serotonin syndrome, caution is advised when citalopram is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see WARNINGS-Serotonin Syndrome). The concomitant use of citalopram with other SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS - Drug Interactions).

Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of citalopram with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS - Serotonin Syndrome).

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 citalopram tablets are not recommended.

Monoamine Oxidase Inhibitors (MAOIs) - See CONTRAINDICATIONS and WARNINGS.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.) - Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when citalopram is initiated or discontinued.

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

Lithium - Coadministration of citalopram tablets (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 citalopram tablets and lithium are coadministered.

Pimozide - In a controlled study, a single dose of pimozide 2 mg co-administered with citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

Theophylline - Combined administration of citalopram tablets (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 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 citalopram tablets 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 citalopram tablets (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 citalopram tablets (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 citalopram tablets (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 citalopram tablets 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 citalopram tablets 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 citalopram tablets (40 mg/day for 10 days) with the TCA 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 TCAs with citalopram tablets.

Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and citalopram tablets.

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/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 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses \geq 32 mg/kg/day, approximately 5 times the 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 MRHD of 60 mg/day on a body surface area (mg/m²) basis. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental, no-effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m² 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/m² 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/m² basis. The no-effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m² basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses \geq 24 mg/kg/day, approximately 4 times the MRHD on a mg/m² 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.

Nonteratogenic Effects

Neonates exposed to citalopram and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying.

These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1—2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with citalopram during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Labor and Delivery

The effect of citalopram tablets 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 breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or citalopram tablets therapy should take into account the risks of citalopram exposure for the infant and the benefits of citalopram tablets treatment for the mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with citalopram tablets, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of citalopram tablets in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

Of 4422 patients in clinical studies of citalopram tablets, 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 citalopram tablets in clinical trials received daily doses between 20 and 40 mg (see DOSAGE AND ADMINISTRATION).

SSRIs and SNRIs, including citalopram, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see

PRECAUTIONS, Hyponatremia).

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 citalopram tablets 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 citalopram tablets 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 citalopram tablets 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 citalopram tablets-treated patients at a rate at least twice that of placebo) are shown in TABLE 2. 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 2 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%	less than 1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	less than 1%
Vomiting	1%	0%
Central and Peripheral Nervous System Disorders		
Dizziness	2%	less than 1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	less than 1%

Adverse Events Occurring at an Incidence of 2% or More Among Citalopram-Treated Patients

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received citalopram tablets 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 citalopram tablets and for which the incidence in patients treated with citalopram tablets were 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 citalopram 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 3).

TABLE 3 Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*

Body System/Adverse Event	(Percentage of Patients Reporting Event)	
	Citalopram Tablets (N=1063)	Placebo (N=446)
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central and 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%	less than 1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorder		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea ¹	3%	2%
Libido Decreased	2%	less than 1%
Yawning	2%	less than 1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	less than 1%
Urogenital		
Ejaculation Disorder ^{2,3}	6%	1%
Impotence ³	3%	less than 1%

* Events reported by at least 2% of patients treated with citalopram tablets are reported, except for the following events which had an incidence on placebo greater than or equal to citalopram tablets: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.

1 Denominator used was for females only (N=638 citalopram tablets; N=252 placebo).

2 Primarily ejaculatory delay.

3 Denominator used was for males only (N=425 citalopram tablets; N=194 placebo).

Dose Dependency of Adverse Events

The potential relationship between the dose of citalopram tablets administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or citalopram tablets 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response (p less than 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 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 citalopram tablets in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	Citalopram Tablets (425 males)	Placebo (194 males)
Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
Libido Decreased	3.8% (males only)	less than 1% (males only)
Impotence	2.8% (males only)	less than 1% (males only)

In female depressed patients receiving citalopram tablets, 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

Citalopram tablets 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 citalopram hydrobromide treatment. In addition, a comparison of supine and standing vital sign measures for citalopram tablets and placebo treatments indicated that citalopram tablets treatment is not associated with orthostatic changes.

Weight Changes

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

Laboratory Changes

Citalopram tablets 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 citalopram tablets treatment.

ECG Changes

Electrocardiograms from citalopram tablets (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 citalopram tablets 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 Citalopram Tablets

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 citalopram tablets 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 3 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 citalopram tablets, 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 Postmarketing Evaluation of Citalopram Tablets

It is estimated that over 30 million patients have been treated with citalopram since market introduction. Although no causal relationship to citalopram treatment has been found, the following adverse events have been reported to be temporally associated with citalopram treatment, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, glaucoma, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, ventricular arrhythmia, torsade de pointes, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Citalopram hydrobromide is not a controlled substance.

Physical and Psychological Dependence

Animal studies suggest that the abuse liability of citalopram tablets is low. Citalopram tablets have not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with citalopram tablets 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 citalopram 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

In clinical trials of citalopram, there were reports of citalopram overdose, including overdoses of up to 2000 mg, with no associated fatalities. During the postmarketing evaluation of citalopram, citalopram overdoses, including overdoses of up to 6000 mg, have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely reported.

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 very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

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 citalopram tablets.

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

Citalopram tablets 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.

Citalopram tablets 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. Citalopram tablets should be used with caution in patients with severe renal impairment.

Treatment of Pregnant Women During the Third Trimester

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

Maintenance Treatment

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Systematic evaluation of citalopram tablets 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 citalopram tablets (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 citalopram tablets 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.

Discontinuation of Treatment with Citalopram Tablets

Symptoms associated with discontinuation of citalopram and other SSRIs and SNRIs have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of citalopram tablets therapy. Similarly, at least 14 days should be allowed after stopping citalopram tablets before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

HOW SUPPLIED

Citalopram tablets are supplied as:

10 mg Tablets – Peach coloured, biconvex, round shaped film coated tablets debossed with ‘A’ on one side and ‘05’ on the other side.

Bottles of 30	NDC 65862-005-30
Bottles of 60	NDC 65862-005-60
Bottles of 90	NDC 65862-005-90
Bottles of 100	NDC 65862-005-01
Bottles of 500	NDC 65862-005-05
10 x 10 Unit Dose	NDC 65862-005-10
30 Unit-of-use packaging	NDC 65862-005-32

20 mg Tablets – Light pink coloured, biconvex, capsule shaped film coated tablets debossed with ‘A’ on one side and with a score line in between ‘0’ and ‘6’ on other side.

Bottles of 30	NDC 65862-006-30
Bottles of 60	NDC 65862-006-60
Bottles of 90	NDC 65862-006-90
Bottles of 100	NDC 65862-006-01
Bottles of 500	NDC 65862-006-05
10 x 10 Unit Dose	NDC 65862-006-10
30 Unit-of-use packaging	NDC 65862-006-32

40 mg Tablets – White coloured, biconvex, capsule shaped film coated tablets debossed with ‘A’ on one side and with a score line in between ‘0’ and ‘7’ on other side.

Bottles of 30	NDC 65862-007-30
Bottles of 60	NDC 65862-007-60
Bottles of 90	NDC 65862-007-90
Bottles of 100	NDC 65862-007-01
Bottles of 500	NDC 65862-007-05
10 x 10 Unit Dose	NDC 65862-007-10
30 Unit-of-use packaging	NDC 65862-007-32

Manufactured for:
Aurobindo Pharma USA, Inc.
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Dayton, NJ 08810

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India

Revised: 02/2009

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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 2020 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 dogs has not been directly examined because DCT is rapidly converted to DDCT in that species.

Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. Talk to your, or your family member's, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.
2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying

- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.
- Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- Antidepressant medicines have other side effects. Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- Not all antidepressant medicines prescribed for children are FDA approved for use in children. Talk to your child's healthcare provider for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India

Revised: 02/2009

NDC 65862-005-01

Citalopram Tablets, USP

10 mg

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

Rx only

100 Tablets

AUROBINDO

Each tablet contains:

Citalopram hydrobromide USP equivalent to 10 mg citalopram base.

Keep this and all drugs out of the reach of children.

See package insert for full prescribing information.

Dispense in tight container as described in the USP.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Revised: 09/2008

Manufactured for: Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

Manufactured by: Aurobindo Pharma Limited
Hyderabad-500 072, India

Batch :

Expiry :

P1404156

N3 65862 - 005 - 01 4

Sentra AM™ PRODUCT INFORMATION Sentra AM (U.S. patent pending) capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary blend of amino acids and polyphenol ingredients in specific proportions, for the nutritional management of the metabolic processes of fatigue and cognitive disorders (FCD). Must be administered under physician supervision. Medical Foods Medical Food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician's care for the nutritional management of diseases in patients with particular medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a food which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical Foods are complex formulated products, requiring sophisticated and exacting technology. Sentra AM has been developed, manufactured, and labeled in accordance with both the statutory and the FDA regulatory definition of a Medical Food. Sentra AM must be used while the patient is under the ongoing care of a physician. FATIGUE AND COGNITIVE DISORDERS (FCD) FCD as a Metabolic Deficiency Disease A critical component of the definition of a Medical Food is the requirement for a distinctive nutritional deficiency. FDA scientists have proposed a physiologic definition of a distinctive nutritional deficiency as follows: "the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences, recognized that different or distinctive physiologic requirements may exist for certain persons with "special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions and drug therapies. Thus, the distinctive nutritional needs associated with a disease reflect the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism, and excretion." It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, if a patient with fatigue and cognitive

disorders responds to a choline formulation by decreasing perceived fatigue and increasing cognitive function, a deficiency of choline is assumed to exist. Patients with fatigue and cognitive disorders are known to have nutritional deficiencies of choline, flavonoids, and certain antioxidants. Patients with fatigue and cognitive disorders frequently exhibit reduced plasma levels of choline and have been shown to respond to oral administration of a choline formulation. Research has shown that choline reduced diets result in a fall of circulating choline. Patients with fatigue and cognitive disorders sometimes have activation of the degradation pathways that increase the turnover of choline leading to a reduced level of production of acetylcholine for a given choline blood level. Research has also shown that a genetic predisposition to accelerated degradation of choline can lead to increased precursor requirements in certain patients with fatigue and cognitive disorders. Choline is required to fully potentiate acetylcholine synthesis by brain neurons. A deficiency of choline leads to reduced acetylcholine production by the neurons. Patients with fatigue and cognitive disorders frequently consume diets that are choline deficient. Flavonoids potentiate the production of acetylcholine by the neurons thereby reducing fatigue and cognitive impairment. Diets deficient in flavonoid rich foods result in inadequate flavonoid concentrations, impeding acetylcholine production in certain patients with fatigue and cognitive disorders. Acetylcholine in pre-synaptic and post-synaptic ganglia is necessary for neuronal function. Provision of choline and flavonoids with antioxidants, in specific proportions can restore the production of beneficial acetylcholine, thereby reducing fatigue and improving cognitive function.

PRODUCT DESCRIPTION Primary Ingredients Sentra AM consists of a proprietary blend of amino acids, cocoa, and flavonoids in specific proportions. These ingredients fall into the category of “Generally Regarded as Safe” (GRAS) as defined by the Food and Drug Administration (FDA) (Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act). A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition of safety through widespread usage and agreement of that safety by experts in the field. Many ingredients have been determined by the U.S. Food and Drug Administration (FDA) to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186. Amino Acids Amino Acids are the building blocks of protein. All amino acids are GRAS listed as they have been ingested by humans for thousands of years. The doses of the amino acids, particularly choline, in Sentra AM are equivalent to those found in the usual human diet; however the formulation uses specific ratios of the key ingredients to elicit a therapeutic response. Patients with fatigue and cognitive disorders may require an increased amount of certain amino acids that cannot be obtained from normal diet alone. Choline, for example, is an obligatory amino acid. The body cannot make choline and must obtain choline from the diet. Choline is needed to produce acetylcholine. Acetylcholine is required to reduce fatigue and improve cognitive function. Patients with fatigue and cognitive disorders have altered choline metabolism. Some patients with fatigue and cognitive disorders have a resistance to the metabolism of choline that is similar to the mechanism found in insulin resistance. Patients with fatigue and cognitive disorders cannot acquire sufficient choline from the diet without ingesting a prohibitively large amount of calories, particularly calories from protein. Flavonoids Flavonoids are a group of phytochemical compounds found in all vascular plants including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, cocoa, red wine, and green tea are directly related to their flavonoid content. The specially formulated flavonoids found in Sentra AM cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response. Physical Description Sentra AM is a yellow to light brown powder. Sentra AM contains L-Glutamic Acid, Choline Bitartrate, Cocoa, Acetylcarnitine, and Hawthorn Berry. Other Ingredients Sentra AM contains the following inactive or other ingredients as fillers, excipients, and colorings: magnesium stearate, microcrystalline cellulose, Maltodextrin NF, gelatin (as the capsule material).

CLINICAL PHARMACOLOGY Mechanism of Action Sentra AM acts by restoring and maintaining the balance of the neurotransmitter acetylcholine that is associated with fatigue and cognitive disorders.

Metabolism The amino acids in Sentra AM are primarily absorbed by the stomach and small intestines. All cells metabolize the amino acids in Sentra AM. Circulating choline blood levels determine the production of acetylcholine. **Excretion** Sentra AM is not an inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4. These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of roughly 50% of drugs. Amino acids do not appear to have an effect on drug metabolizing enzymes. Sentra AM does not directly interact with prescription drugs. Pharmaceutical administration may allow for lowering of the drug dose under physician supervision.

INDICATIONS FOR USE Sentra AM is intended for the clinical nutritional management of the metabolic processes associated with fatigue and cognitive disorders. - Chronic fatigue - Cognitive impairment - Fibromyalgia

CLINICAL EXPERIENCE Administrations of Sentra AM has demonstrated significant functional improvements when used for the nutritional management of the metabolic processes associated with fatigue and cognitive disorders. Administration of Sentra AM results in the reduction of fatigue and cognitive impairment. Sentra AM has no effect on normal blood pressure.

PRECAUTIONS AND CONTRAINDICATIONS Sentra AM is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of Sentra AM.

ADVERSE REACTIONS Oral administration of choline at high doses up to 15 grams daily is generally well tolerated. The most common adverse reactions of higher doses — from 15 to 30 grams daily — are nausea, abdominal cramps, and diarrhea. Some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each Sentra AM capsule does not exceed 400 mg.

DRUG INTERACTIONS Sentra AM does not directly influence the pharmacokinetics of prescription drugs. Clinical experience has shown that administration of Sentra AM may allow for lowering the dose of co-administered drugs under physician supervision.

OVERDOSE There is a negligible risk of overdose with Sentra AM as the total dosage of amino acids in a one month supply (60 capsules) is less than 25 grams. Overdose symptoms may include diarrhea, weakness, and nausea. **POST-MARKETING SURVEILLANCE** Post-marketing surveillance has shown no significant adverse reactions. Reported cases of mild rash and itching may have been associated with allergies to Sentra AM flavonoid ingredients, including cinnamon, cocoa, and chocolate. The reactions were transient in nature and subsided within 24 hours.

DOSAGE AND ADMINISTRATION **Recommended Administration** For the nutritional management of the metabolic processes in patients with fatigue and cognitive disorders. Take (2) capsules one to three times daily or as directed by physician. As with most amino acid formulations Sentra AM should be taken between meals without food to increase the absorption of key ingredients.


How Supplied Sentra AM is supplied in opaque orange and white, size 0 capsules in bottles of 60 capsules. **Physician Supervision** Sentra AM is a Medical Food product available by prescription only and must be used while the patient is under ongoing physician supervision. U.S. patent pending. Manufactured by Arizona Nutritional Supplements, Inc. Chandler AZ 85225 Distributed by Physician Therapeutics LLC, Los Angeles, CA 90077. www.ptlcentral.com Copyright 2003-2006, Physician Therapeutics LLC, all rights reserved NDC # 68405-1002-02

Storage Store at room temperature, 59-86OF (15-30OC) Protect from light and moisture. Sentra AM is supplied to physicians in a recyclable plastic bottle with a child-resistant cap.

PHYSICIAN THERAPEUTICS SENTRA AM Medical Food Rx only 60 Capsules Directions for use: Must be administered under medical supervision. For adults only. As a Medical Food, take two (2) capsules in the morning on an empty stomach or as directed by your medical practitioner. For the dietary management of chronic fatigue syndromes. Contains no added sugar, starch, wheat, yeast, preservatives, artificial color or flavor. **Storage:** Keep tightly closed in a cool dry place 8-320 C (45-

900F), relative humidity, below 50%. Warning: Keep this product out of the reach of children. NDC# 68405-1002-02 Ingredients: Each serving (2 capsules) contains: Proprietary Amino Acid Blend Choline Bitartrate, L-Glutamic Acid, Cocoa Extract (fruit), Acetyl L-Carnitine HCl Proprietary Herbal Blend Ginkgo Biloba (leaves), Hawthorn Berry (fruit), Dextrose Other Ingredients: Gelatin, Cellulose, Dicalcium Phosphate, Silicon Dioxide and Vegetable Magnesium Stearate. Distributed by: Physician Therapeutics LLC, Los Angeles, CA 90077 www.ptlcentral.com Patent Pending

68405-012-26 For the Dietary Management of Fatigue and Cognitive Disorders. Two capsules in the morning or as directed by physician. See product label and insert. Sentra AM Medical Food PHYSICIAN THERAPEUTICS Sentra AM + Citalopram 10 mg A Convenience Pakced Medical Food and Drug Sentralopram AM-10 PHYSICIAN THERAPEUTICS > Sentra AM 60 Capsules > Citalopram 10 mg 30 Tablets Rx Only NDC # 68405-012-26 of this co-pack No Refills Without Physician Authorization As prescribed by physician. See product label and product information insert. Citalopram 10 mg Rx Drug Manufactured and Distributed by Physician Therapeutics, A Division of Targeted Medical Pharma Inc. Los Angeles, CA 90077 www.ptlcentral.com B-NDC# 68405-8012-26



68405-1002-02

Directions for use:
Must be administered under medical supervision.

For adults only. As a Medical Food, take two (2) capsules in the morning on an empty stomach or as directed by your medical practitioner.

For the dietary management of chronic fatigue syndromes.

Contains no added sugar, starch, wheat, yeast, preservatives, artificial color or flavor.

Storage:
Keep tightly closed in a cool dry place 8-32°C (45-90°F), relative humidity, below 50%.

Warning: Keep this product out of the reach of children.

NDC# 68405-1002-02



SENTRA AM

Medical Food

Rx only

60 Capsules

Ingredients:

Each serving (2 capsules) contains:
Proprietary Amino Acid Blend
Choline Bitartrate,
L-Glutamic Acid,
Cocoa Extract (fruit)
Acetyl L-Carnitine HCl
Proprietary Herbal Blend
Ginkgo Biloba (leaves),
Hawthorn Berry (fruit),
Dextrose

Other Ingredients: Gelatin, Cellulose, Dicalcium Phosphate, Silicon Dioxide and Vegetable Magnesium Stearate.

Distributed by:
Physician Therapeutics LLC, Los Angeles, CA 90077
www.ptlcentral.com
Patent Pending

52959-0603-30

CAUTION: Federal law PROHIBITS the transfer of this drug to anyone other than the person to whom prescribed and prohibits dispensing without a prescription unless OTC. See insert for add'l Rx info KEEP OUT OF REACH OF CHILDREN. Store in a cool dry place at 68 to 77 degrees F.

CITALOPRAM HYDRO. 10mg TABLET

Lot #: CIT00ZT



#30

Mfg: AUROBINDO

Exp: 09/11 Compare to: Celexa

Mfg. NDC: 65862-0005-05

Take as directed by your Doctor or
See insert for usual dosage information

CITALOPRAM HYDRO. 10mg TABLET	
52959-0603-30	Qty #30
09/11	Lot CIT00ZT
Celexa	65862-0005-05

CITALOPRAM HYDRO. 10mg TABLET	
52959-0603-30	Qty #30
09/11	Lot CIT00ZT
Celexa	65862-0005-05

CITALOPRAM HYDRO. 10mg TABLET	
52959-0603-30	Qty #30
09/11	Lot CIT00ZT
Celexa	65862-0005-05

CITALOPRAM HYDRO. 10mg TABLET	
52959-0603-30	Qty #30
09/11	Lot CIT00ZT
Celexa	65862-0005-05

Repack: HJ Harkins Co., Inc. Nipomo, CA 93444

A Convenience Packed Medical Food & Drug

Sentralopram AM-10TM



- ▶ **Sentra AMTM 60 Capsules**
- ▶ **Citalopram 10 mg 30 Tablets**

No Refills Without
Physician Authorization

Rx Only
NDC# 68405-012-26
of this co-pack

SENTRALOPRAM AM-10

citalopram hydrobromide, choline kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68405-012
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68405-012-26	1 in 1 KIT		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 BOTTLE	30
Part 2	1 BOTTLE	60

Part 1 of 2**CITALOPRAM**

citalopram hydrobromide tablet

Product Information

Item Code (Source)	NDC:52959-603(NDC:65862-005)
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CITALOPRAM HYDROBROMIDE (UNII: I1E9D14F36) (CITALOPRAM - UNII:0DHU5B8D6V)	CITALOPRAM HYDROBROMIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
COPOVIDONE (UNII: D9C330MD8B)	
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE 2910 (6 MPAS) (UNII: 0WZ8WG20P6)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	orange (Peach)	Score	no score
Shape	ROUND (Biconvex)	Size	5mm
Flavor		Imprint Code	A;05

Contains**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52959-603-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077031	07/07/2011	

Part 2 of 2**SENTRA AM**

choline capsule

Product Information

Route of Administration	ORAL
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Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CHOLINE (UNII: N91BDP6H0X) (CHOLINE - UNII:N91BDP6H0X)	CHOLINE	250 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MALTODEXTRIN (UNII: 7CVR7L4A2D)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics

Color	orange (ORANGE)	Score	no score
Shape	CAPSULE	Size	21mm
Flavor		Imprint Code	;
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Medical Food		07/07/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		07/07/2011	

Labeler - Physician Therapeutics LLC (931940964)

Establishment

Name	Address	ID/FEI	Business Operations
Aurobindo Pharma Limited		918917642	manufacture

Establishment

Name	Address	ID/FEI	Business Operations
H.J. Harkins Company, Inc.		147681894	repack

Establishment

Name	Address	ID/FEI	Business Operations
Targeted Medical Pharma Inc.		126962740	manufacture

Revised: 8/2011

Physician Therapeutics LLC