For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

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SERENATA

(Sertraline Hydrochloride 50mg and 100mg Tablet I.P.)

COMPOSITION

SERENATA 50

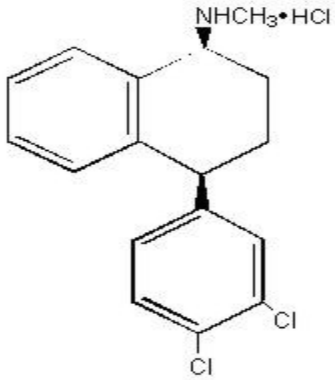
Each Film coated Tablet contains
Sertraline hydrochloride I.P. equivalent to Sertraline 50mg
Colour: Titanium Dioxide I.P.

SERENATA 100

Each Film coated Tablet contains
Sertraline hydrochloride I.P. equivalent to Sertraline 100mg
Colour: Titanium Dioxide I.P.

DESCRIPTION

Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NC_{l2}$**.**HCl is represented by the following structural formula:



Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to down regulate brain norepinephrine

receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability–In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and C_{max} values were 114.8% and 120.6%, respectively. 90% confidence intervals (CI) were within the range of 80-125% with the exception of the upper 90% CI limit for C_{max} which was 126.5%.

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration (T_{max}) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, T_{max} was slightly prolonged from 5.9 hours to 7.0 hours with food.

Metabolism–Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), C_{max} and C_{min}, with about a 5-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Protein Binding–*In vitro* protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-

desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol.

Pediatric Pharmacokinetics–Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of major depressive disorder or obsessive-compulsive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6-12 year old group exhibited a mean sertraline AUC (0-24 hr) of 3107 ng-hr/mL, mean C_{max} of 165 ng/mL, and mean half-life of 26.2 hr. The 13-17 year old group exhibited a mean sertraline AUC (0-24 hr) of 2296 ng-hr/mL, mean C_{max} of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0-24 hr) of 2570 ng-hr/mL, mean C_{max} of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6-12 year olds and the 13-17 year olds showed about 22% lower AUC (0-24 hr) and C_{max} values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels.

Age–Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady-state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.

Liver Disease–As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.

Renal Disease–Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLcr=30-60 mL/min), moderate to severe (CLcr=10-29 mL/min) or severe (receiving hemodialysis) renal impairment (N=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (N=12) with no

renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment

INDICATIONS AND USAGE
Sertraline is indicated for the treatment of depression.

DOSAGE AND ADMINISTRATION
For the treatment and prevention of recurrence of depression, an initial dosage of 50mg once daily increased if necessary, in increment of 50mg at interval of at least a week to a maximum of 200mg daily.

CONTRAINDICATIONS
The use of MAOIs intended to treat psychiatric disorders with Sertraline hydrochloride or within 14 days of stopping treatment with Sertraline hydrochloride is contraindicated because of an increased risk of serotonin syndrome. The use of Sertraline hydrochloride within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.

Starting Sertraline hydrochloride in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.

Concomitant use in patients taking pimozide is contraindicated.

Sertraline is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients of tablet.

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 strongest 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
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥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.

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 Sertraline 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, anddepression. It should be noted that Sertraline is not approved for use in treating bipolar depression.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Sertraline, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Sertraline with MAOIs intended to treat psychiatric disorders is contraindicated. Sertraline should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or

intravenous methylene blue in a patient taking Sertraline. Sertraline should be discontinued before initiating treatment with the MAOI.

If concomitant use of Sertraline with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Sertraline and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including Sertraline may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

PRECAUTIONS

General

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in approximately 0.4% of sertraline hydrochloride treated patients.

Weight Loss

Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.

Seizure

Sertraline has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with Sertraline in the development program for major depressive disorder. However, 4 patients out of approximately 1800 (220 <18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, Sertraline should be introduced with care in patients with a seizure disorder.

Discontinuation of Treatment with Sertraline

During marketing of Sertraline 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 Sertraline. 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.

Abnormal Bleeding
SSRIs and SNRIs, including Sertraline, may increase the risk of bleeding events ranging from ecchymoses, hematomas, epistaxis, petechiae, and gastrointestinal hemorrhage to life-threatening hemorrhage. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants or other drugs known to affect platelet function may add to this 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.

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

Weak Uricosuric Effect
Sertraline hydrochloride is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Use in Patients with Concomitant Illness
Clinical experience with Sertraline in patients with certain concomitant systemic illness is limited. Caution is advisable in using Sertraline in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received Sertraline in double-blind trials were evaluated and the data indicate that Sertraline is not associated with the development of significant ECG abnormalities.

During post-marketing use of sertraline, cases of QTc prolongation and Torsade de Pointes (TdP) have been reported. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP. Therefore Sertraline should be used with caution in patients with risk factors for QTc prolongation.

Sertraline administered in a flexible dose range of 50 to 200 mg/day (mean dose of 89 mg/day) was evaluated in a post-marketing, placebo-controlled trial of 372 randomized subjects with a DSM-IV diagnosis of major depressive disorder and recent history of myocardial infarction or unstable angina requiring hospitalization. Exclusions from this trial included, among others, patients with uncontrolled hypertension, need for cardiac surgery, history of CABG within 3 months of index event, severe or symptomatic bradycardia, non-atherosclerotic cause of angina, clinically significant renal impairment (creatinine > 2.5 mg/dl), and clinically significant hepatic dysfunction. Sertraline treatment initiated during the acute phase of recovery (within 30 days

post-MI or post-hospitalization for unstable angina) was indistinguishable from placebo in this study on the following week 16 treatment endpoints: left ventricular ejection fraction, total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, CHF, MI, tachycardia, bradycardia, and changes in BP), and major cardiovascular events involving death or requiring hospitalization (for MI, CHF, stroke, or angina).

Sertraline is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, C_{max} and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.

Since Sertraline is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing Sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetic results, there is no need for dosage adjustment in patients with renal impairment.

Interference with Cognitive and Motor Performance
In controlled studies, Sertraline did not cause sedation and did not interfere with psychomotor performance.

Hyponatremia
Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Sertraline. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). 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. Discontinuation of Sertraline 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.

Platelet Function
There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking Sertraline. While there have been reports of abnormal bleeding or purpura in several patients taking Sertraline, it is unclear whether Sertraline had a causative role.

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.

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

Patients should be advised that taking Sertraline can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

Patients should be told that although Sertraline has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Therefore, patients should be told that until they learn how they respond to Sertraline they should be careful doing activities when they need to be alert, such as driving a car or operating machinery.

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

Patients should be told that while no adverse interaction of Sertraline with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product.

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

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

Laboratory Tests

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking sertraline. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of sertraline therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines.

USE IN SPECIFIC POPULATIONS

Alcoholics

Although Sertraline did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of Sertraline and alcohol is not recommended.

Pregnancy

Pregnancy Category C

Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m^2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. There are no adequate and well-controlled studies in pregnant women. Sertraline (sertraline hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Nonteratogenic Effects

Neonates exposed to Sertraline and other SSRIs or serotonin and norepinephrine reuptake inhibitors (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.

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including

Sertraline) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with Sertraline, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis.

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

Nursing Mothers
Published data concerning sertraline levels in breast milk show that small quantity of sertraline and its metabolite N-desmethylsertraline are excreted in milk. Generally negligible to undetectable levels were found in infant serum, with one exception of an infant with serum levels about 50% of the maternal level (but without a noticeable health effect in this infant). To date, no adverse effects on the health of infants nursed by mothers using sertraline have been reported, but a risk cannot be excluded. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefit outweighs the risk.

Pediatric Use
The efficacy of Sertraline for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6-17. Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established. Two placebo controlled trials (n=373) in pediatric patients with MDD have been conducted with Sertraline, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Sertraline in a child or adolescent must balance the potential risks with the clinical need.

The safety of Sertraline use in children and adolescents with OCD, ages 6-18, was evaluated in a 12-week, multicenter, placebo-controlled study with 187 outpatients, ages 6-17, and in a flexible dose, 52 week open extension study of 137 patients, ages 6-18, who had completed the initial 12-week, double-blind, placebo-controlled study. Sertraline was administered at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-18) and then titrated in weekly 25 mg/day or 50 mg/day increments, respectively, to a maximum dose of 200 mg/day based upon clinical response. The mean dose for completers was 157 mg/day. In the acute 12 week pediatric study and in the 52 week study, Sertraline had an adverse event profile generally similar to that observed in adults.

Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age with major depressive disorder or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for.
Approximately 600 patients with major depressive disorder or OCD between 6 and 17 years of age have received Sertraline in clinical trials, both controlled and uncontrolled. The adverse event profile observed in these patients was generally similar to that observed in adult studies with Sertraline. As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of Sertraline. In a pooled analysis of two 10-week, double-blind, placebo-controlled, flexible dose (50-200 mg) outpatient trials for major depressive disorder (n=373), there was a difference in weight change between sertraline and placebo of roughly 1 kilogram, for both children (ages 6-11) and adolescents (ages 12-17), in both cases representing a slight weight loss for sertraline compared to a slight gain for placebo. At baseline the mean weight for children was 39.0 kg for sertraline and 38.5 kg for placebo. At baseline the mean weight for adolescents was 61.4 kg for sertraline and 62.5 kg for placebo. There was a bigger difference between sertraline and placebo in the proportion of outliers for clinically important weight loss in children than in adolescents. For children, about 7% had a weight loss > 7% of body weight compared to none of the placebo patients; for adolescents, about 2% had a weight loss > 7% of body weight compared to about 1% of the placebo patients. A subset of these patients who completed the randomized controlled trials (sertraline n=99, placebo n=122) were continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5 kg was seen during the first eight weeks of treatment for subjects with first exposure to sertraline during the open-label extension study, similar to mean weight loss observed among sertraline treated subjects during the first eight weeks of the randomized controlled trials. The subjects continuing in the open label study began gaining weight compared to baseline by week 12 of sertraline treatment. Those subjects who completed 34 weeks of sertraline treatment (10 weeks in a placebo controlled trial + 24 weeks open label, n=68) had weight gain that was similar to that expected using data from age-adjusted peers. Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.

The risks, if any, that may be associated with Sertraline use beyond 1 year in children and adolescents with OCD or major depressive disorder have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from clinical studies that were 10 to 52 weeks in duration and from the extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use.

Geriatric Use
U.S. geriatric clinical studies of Sertraline in major depressive disorder included 663 Sertraline treated subjects ≥ 65 years of age, of those, 180 were ≥ 75 years of age. No overall differences in the pattern of adverse reactions were observed in the geriatric clinical trial subjects relative to

those reported in younger, and other reported experience has not identified differences in safety patterns between the elderly and younger subjects. As with all medications, greater sensitivity of some older individuals cannot be ruled out. There were 947 subjects in placebo-controlled geriatric clinical studies of Sertraline in major depressive disorder. No overall differences in the pattern of efficacy were observed in the geriatric clinical trial subjects relative to those reported in younger subjects.

Other Adverse Events in Geriatric Patients. In 354 geriatric subjects treated with Sertraline in placebo-controlled trials, the overall profile of adverse events was generally similar to that shown in Tables 2 and 3. Urinary tract infection was the only adverse event not appearing in Tables 2 and 3 and reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials.

SSRIS and SNRIs, including Sertraline, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

Dosage for Hepatically Impaired Patients

The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.

Drug Interactions

Potential Effects of Co administration of Drugs Highly Bound to Plasma Proteins

Because sertraline is tightly bound to plasma protein, the administration of sertraline hydrochloride to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound Sertraline by other tightly bound drugs.

In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either Sertraline (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for Sertraline compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the Sertraline group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when Sertraline therapy is initiated or stopped.

Cimetidine

In a study assessing disposition of Sertraline (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in Sertraline mean AUC (50%), C_{max} (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

Drugs that Prolong the QT Interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g., TdP) is increased with concomitant use of other drugs which prolong the QTc interval (e.g., some antipsychotics and antibiotics).

CNS Active Drugs

In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either Sertraline (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the Sertraline group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the Sertraline group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of Sertraline did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of Sertraline therapy with appropriate adjustments to the lithium dose.

In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozide AUC and C_{max} of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of Sertraline and pimozide should be contraindicated.

Results of a placebo-controlled trial in normal volunteers suggest that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, at this time, it is recommended that plasma phenytoin concentrations be monitored following initiation of Sertraline therapy with appropriate adjustments to the phenytoin dose, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant medications.

The effect of Sertraline on valproate levels has not been evaluated in clinical trials. In the absence of such data, it is recommended that plasma valproate levels be monitored following initiation of Sertraline therapy with appropriate adjustments to the valproate dose.

The risk of using Sertraline in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Sertraline and such drugs is required.

There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder and social anxiety disorder to Sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which

should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Drugs Metabolized by P450 3A4

In three separate *in vivo* interaction studies, sertraline was coadministered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and C_{max} were reduced by about 35%).

Drugs Metabolized by P450 2D6

Many drugs effective in the treatment of major depressive disorder, e.g., the SSRIs, including sertraline, and most tricyclic antidepressant drugs effective in the treatment of major depressive disorder inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressant drugs effective in the treatment of major depressive disorder and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the drugs effective in the treatment of major depressive disorder in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with Sertraline may require lower doses than usually prescribed for the other drug. Furthermore, whenever Sertraline is withdrawn from co-therapy, an increased dose of the co-administered drug may be required.

Triptans

There have been rare post marketing reports of serotonin syndrome with use of an SNRI or an SSRI and a triptan. If concomitant treatment of SNRIs and SSRIs, including Sertraline, with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Sumatriptan

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

Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)

The extent to which SSRI–TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with Sertraline, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with Sertraline.

Hypoglycemic Drugs
In a placebo-controlled trial in normal volunteers, administration of Sertraline for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. Sertraline administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

Atenolol
Sertraline (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.

Digoxin
In a placebo-controlled trial in normal volunteers, administration of Sertraline for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.

Microsomal Enzyme Induction
Preclinical studies have shown Sertraline to induce hepatic microsomal enzymes. In clinical studies, Sertraline was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

Drugs that interfere with hemostasis (Non-selective 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 this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Sertraline is initiated or discontinued.

ADVERSE REACTIONS

During its premarketing assessment, multiple doses of Sertraline were administered to over 4000 adult subjects as of February 18, 2000. The conditions and duration of exposure to Sertraline varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-

dose and titration studies, and studies for multiple indications, including major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder.

Untoward events associated with this exposure were 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 untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of Sertraline who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving Sertraline. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that 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 side effect incidence rate in the population studied.

Incidence in Placebo-Controlled Trials

Table 2 enumerates the most common treatment-emergent adverse events associated with the use of Sertraline (incidence of at least 5% for Sertraline and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder in placebo-controlled clinical trials. Most patients in major depressive disorder/other*, OCD, panic disorder, PTSD and social anxiety disorder studies received doses of 50 to 200 mg/day. Patients in the PMDD study with daily dosing throughout the menstrual cycle received doses of 50 to 150 mg/day, and in the PMDD study with dosing during the luteal phase of the menstrual cycle received doses of 50 to 100 mg/day. Table 3 enumerates treatment-emergent adverse events that occurred in 2% or more of adult patients treated with Sertraline and with incidence greater than placebo who participated in controlled clinical trials comparing Sertraline with placebo in the treatment of major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder. Table 3 provides combined data for the pool of studies that are provided separately by indication in Table 2.

TABLE 2

MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Percentage of Patients Reporting Event				
	Major Depressive Disorder/Other*	**OCD**	**Panic Disorder**	**PTSD**

Body System/Adverse Event	Sertraline (N=861)	Placebo (N=853)	Sertraline (N=533)	Placebo (N=373)	Sertraline (N=430)	Placebo (N=275)	Sertraline (N=374)	Placebo (N=376)
Autonomic Nervous System Disorders								
Ejaculation Failure[(1)]	7	<1	17	2	19	1	11	1
Mouth Dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Center. & Periph. Nerv. System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
Dizziness	12	7	17	9	10	10	8	5
General								
Fatigue	11	8	14	10	11	6	10	5
Pain	1	2	3	1	3	3	4	6
Malaise	<1	1	1	1	7	14	10	10
Gastrointestinal Disorders								
Abdominal Pain	2	2	5	5	6	7	6	5
Anorexia	3	2	11	2	7	2	8	2
Constipation	8	6	6	4	7	3	3	3
Diarrhea/Loose Stools	18	9	24	10	20	9	24	15
Dyspepsia	6	3	10	4	10	8	6	6
Nausea	26	12	30	11	29	18	21	11
Psychiatric Disorders								
Agitation	6	4	6	3	6	2	5	5
Insomnia	16	9	28	12	25	18	20	11
Libido Decreased	1	<1	11	2	7	1	7	2

	PMDD Daily Dosing		PMDD Luteal Phase Dosing		Social Anxiey Disorder	
Body System/Adverse Event	**Sertraline (N=121)**	**Placebo (N=122)**	**Sertraline (N=136)**	**Placebo (N=127)**	**Sertraline (N=344)**	**Placebo (N=268)**
Autonomic Nervous						

System Disorders							
Ejaculation Failure[(1)]	N/A	N/A	N/A	N/A	14	-	
Mouth Dry	6	3	10	3	12	4	
Sweating Increased	6	<1	3	0	11	2	
Center. & Periph. Nerv. System Disorders							
Somnolence	7	<1	2	0	9	6	
Tremor	2	0	<1	<1	9	3	
Dizziness	6	3	7	5	14	6	
General							
Fatigue	16	7	10	<1	12	6	
Pain	6	<1	3	2	1	3	
Malaise	9	5	7	5	8	3	
Gastrointestinal Disorders							
Abdominal Pain	7	<1	3	3	5	5	
Anorexia	3	2	5	0	6	3	
Constipation	2	3	1	2	5	3	
Diarrhea/Loose Stools	13	3	13	7	21	8	
Dyspepsia	7	2	7	3	13	5	
Nausea	23	9	13	3	22	8	
Psychiatric Disorders							
Agitation	2	<1	1	0	4	2	
Insomnia	17	11	12	10	25	10	
Libido Decreased	11	2	4	2	9	3	

[(1)] Primarily ejaculatory delay. Denominator used was for male patients only (N=271 Sertraline major depressive disorder/other*; N=271 placebo major depressive disorder/other*; N=296 Sertraline OCD; N=219 placebo OCD; N=216 Sertraline panic disorder; N=134 placebo panic disorder; N=130 Sertraline PTSD; N=149 placebo PTSD; No male patients in PMDD studies; N=205 Sertraline social anxiety disorder; N=153 placebo social anxiety disorder). *Major depressive disorder and other premarketing controlled trials.

[2] The luteal phase and daily dosing PMDD trials were not designed for making direct comparisons between the two dosing regimens. Therefore, a comparison between the two dosing regimens of the PMDD trials of incidence rates shown in Table 2 should be avoided.

TABLE 3: TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Percentage of Patients Reporting Event Major Depressive Disorder/Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined

Body System/Adverse Event**	Sertraline (N=2799)	Placebo (N=2394)
Autonomic Nervous System Disorders		
Ejaculation Failure[1]	14	1
Mouth Dry	14	8
Sweating Increased	7	2
Center. & Periph. Nerv. System Disorders		
Somnolence	13	7
Dizziness	12	7
Headache	25	23
Paresthesia	2	1
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	6	4
Diarrhea/Loose Stools	20	10
Dyspepsia	8	4
Nausea	25	11
Vomiting	4	2
General		
Fatigue	12	7
Psychiatric Disorders		
Agitation	5	3
Anxiety	4	3
Insomnia	21	11
Libido Decreased	6	2
Nervousness	5	4
Special Senses		
Vision Abnormal	3	2

[1] Primarily ejaculatory delay. Denominator used was for male patients only (N=1118 Sertraline; N=926 placebo).

*Major depressive disorder and other premarketing controlled trials.

**Included are events reported by at least 2% of patients taking Sertraline except the following events, which had an incidence on placebo greater than or equal to Sertraline: abdominal pain,

back pain, flatulence, malaise, pain, pharyngitis, respiratory disorder, upper respiratory tract infection.

Associated with Discontinuation in Placebo-Controlled Clinical Trials

Table 4 lists the adverse events associated with discontinuation of sertraline hydrochloride treatment (incidence at least twice that for placebo and at least 1% for Sertraline in clinical trials in major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder.

TABLE 4

MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Major Depressive Disorder/Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined (N=2799)	Major Depressive Disorder/ Other* (N=861)	OCD (N=533)	Panic Disorder (N=430)	PTSD (N=374)	PMDD Daily Dosing (N=121)	PMDD Luteal Phase Dosing (N=136)	Social Anxiety Disorder (N=344)
Abdominal Pain	–	–	–	–	–	–	–	1%
Agitation	–	1%	–	2%	–	–	–	–
Anxiety	–	–	–	–	–	–	–	2%
Diarrhea/ Loose Stools	2%	2%	2%	1%	–	2%	–	–
Dizziness	–	–	1%	–	–	–	–	–
Dry Mouth	–	1%	–	–	–	–	–	–
Dyspepsia	–	–	–	1%	–	–	–	–
Ejaculation Failure(1)	1%	1%	1%	2%	–	N/A	N/A	2%
Fatigue	–	–	–	–	–	–	–	2%
Headache	1%	2%	–	–	1%	–	–	2%
Hot Flushes	–	–	–	–	–	–	1%	–
Insomnia	2%	1%	3%	2%	–	–	1%	3%
Nausea	3%	4%	3%	3%	2%	2%	1%	2%
Nervousness	–	–	–	–	–	2%	–	–
Palpitation	–	–	–	–	–	–	1%	–
Somnolence	1%	1%	2%	2%	–	–	–	–
Tremor	–	2%	–	–	–	–	–	–

(1) Primarily ejaculatory delay. Denominator used was for male patients only (N=271 major depressive disorder/other*; N=296 OCD; N=216 panic disorder; N=130 PTSD; No male patients in PMDD studies; N=205 social anxiety disorder). *Major depressive disorder and other premarketing controlled trials.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic

treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

Table 5 below displays the incidence of sexual side effects reported by at least 2% of patients taking Sertraline in placebo-controlled trials.

TABLE 5

Adverse Event	Sertraline	Placebo
Ejaculation failure* (primarily delayed ejaculation)	14%	1%
Decreased libido**	6%	1%

* Denominator used was for male patients only (N=1118 Sertraline; N=926 placebo)

**Denominator used was for male and female patients (N=2799 Sertraline; N=2394 placebo)

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline 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.

Other Adverse Events in Pediatric Patients

In over 600 pediatric patients treated with Sertraline, the overall profile of adverse events was generally similar to that seen in adult studies. However, the following adverse events, from controlled trials, not appearing in Tables 2 and 3, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate (N=281 patients treated with Sertraline): fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis and purpura.

Other Events Observed during the Premarketing Evaluation of sertraline hydrochloride

Following is a list of treatment-emergent adverse events reported during premarketing assessment of Sertraline in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of Sertraline who experienced an event of the type cited on at least one occasion while receiving Sertraline. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to Sertraline treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with Sertraline, 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 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the Precautions section.

Autonomic Nervous System Disorders–*Frequent:* impotence; *Infrequent:* flushing, increased saliva, cold clammy skin, mydriasis; *Rare:* pallor, angle-closure glaucoma, priapism, vasodilation.

Body as a Whole–General Disorders – *Rare:* allergic reaction, allergy.

Cardiovascular–*Frequent:* palpitations, chest pain; *Infrequent:* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders–*Frequent:* hypertonia, hypoesthesia; *Infrequent:* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare:* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia.

Disorders of Skin and Appendages–*Infrequent:* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare:* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders–*Rare:* exophthalmos, gynecomastia.

Gastrointestinal Disorders–*Frequent:* appetite increased; *Infrequent:* dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare:* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.

General–*Frequent:* back pain, asthenia, malaise, weight increase; *Infrequent:* fever, rigors, generalized edema; *Rare:* face edema, aphthous stomatitis.

Hearing and Vestibular Disorders–*Rare:* hyperacusis, labyrinthine disorder.

Hematopoietic and Lymphatic–*Rare:* anemia, anterior chamber eye hemorrhage.

Liver and Biliary System Disorders–*Rare:* abnormal hepatic function.

Metabolic and Nutritional Disorders–*Infrequent:* thirst; *Rare:* hypoglycemia, hypoglycemia reaction.

Musculoskeletal System Disorders–*Frequent:* myalgia; *Infrequent:* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.

Psychiatric Disorders–*Frequent:* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent:* depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare:* withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive–*Infrequent:* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare:* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders–*Frequent:* rhinitis; *Infrequent:* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare:* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

Special Senses–*Frequent:* tinnitus; *Infrequent:* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare:* xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect.

Urinary System Disorders–*Infrequent:* micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare:* cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury.

Laboratory Tests–In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with sertraline hydrochloride administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Sertraline therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

The safety profile observed with Sertraline treatment in patients with major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder is similar.

Other Events Observed during the Post marketing Evaluation of Sertraline

Reports of adverse events temporally associated with Sertraline that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including Torsade de Pointes arrhythmias), cerebrovascular spasm (including reversible cerebral vasconstriction syndrome and Call-Fleming syndrome), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia,

thrombocytopenia, lupus-like syndrome, serum sickness, diabetes mellitus, hyperglycemia, galactorrhea, hyperprolactinemia, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events—clinical features (which in the majority of cases appeared to be reversible with discontinuation of Sertraline) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Sertraline hydrochloride is not a controlled substance.

Physical and Psychological Dependence

In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of Sertraline, alprazolam, and d-amphetamine in humans, Sertraline did not produce the positive subjective effects indicative of abuse potential, such as euphoria or drug liking, that were observed with the other two drugs. Premarketing clinical experience with Sertraline did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. In animal studies Sertraline does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of Sertraline misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience of 1,027 cases of overdose involving sertraline hydrochloride worldwide, alone or with other drugs, there were 72 deaths (circa 1999).

Among 634 overdoses in which sertraline hydrochloride was the only drug ingested, 8 resulted in fatal outcome, 75 completely recovered, and 27 patients experienced sequelae after overdosage to include alopecia, decreased libido, diarrhea, ejaculation disorder, fatigue, insomnia, somnolence and serotonin syndrome. The remaining 524 cases had an unknown outcome. The most common signs and symptoms associated with non-fatal sertraline hydrochloride overdosage were somnolence, vomiting, tachycardia, nausea, dizziness, agitation and tremor.

The largest known ingestion was 13.5 grams in a patient who took sertraline hydrochloride alone and subsequently recovered. However, another patient who took 2.5 grams of sertraline hydrochloride alone experienced a fatal outcome.

Other important adverse events reported with sertraline hydrochloride overdose (single or multiple drugs) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor, syncope and Torsade de Pointes.

Overdose Management

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.

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

EXPIRY DATE
Do not use later than date of expiry.

STORAGE
Keep in a cool dry place, protected from light.
Keep all tablets away from children.

PRESENTATION
Available in blister pack of 10 tablets

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
"Torrent House", Off Ashram Road,
Ahmedabad - 380 009, INDIA

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