ZOLOFT - sertraline hydrochloride tablet, film coated
REMEDYREPACK INC.

ZOLOFT®(sertraline hydrochloride)Tablets and Oral Concentrate

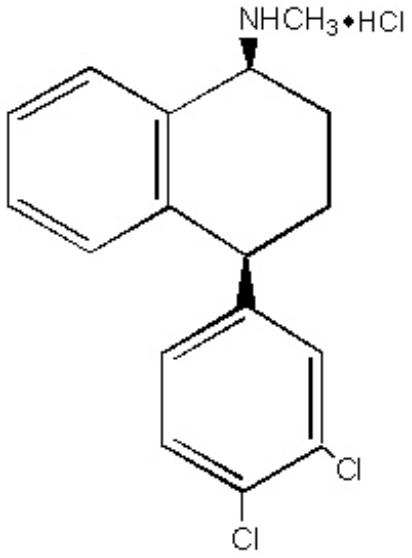
BOXED WARNING

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 ZOLOFT 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. ZOLOFT is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

DESCRIPTION

ZOLOFT® (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 $C_{17}H_{17}NCl_2$•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.

ZOLOFT is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, D & C Yellow #10 aluminum lake (in 25 mg tablet), FD & C Blue #1 aluminum lake (in 25 mg tablet), FD & C Red #40 aluminum lake (in 25 mg tablet), FD & C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide.

ZOLOFT oral concentrate is available in a multidose 60 mL bottle. Each mL of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT). The oral concentrate must be diluted prior to administration (see PRECAUTIONS, Information for Patients and DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

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 ($alpha_1$, $alpha_2$, 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.

In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) 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 Cmax 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 Cmax 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 Cmax 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 Cmax was 25% greater, while the time to reach peak plasma concentration (Tmax) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, Tmax was slightly prolonged from 5.9 hours to 7.0 hours with food.

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), Cmax and Cmin, with about a 5–9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

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 (see PRECAUTIONS).

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 Cmax 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 Cmax 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 Cmax 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 Cmax 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 (see DOSAGE AND ADMINISTRATION).

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.

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 (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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 (see PRECAUTIONS).

The efficacy of ZOLOFT as a treatment for major depressive disorder was established in two placebo-controlled studies in adult outpatients meeting DSM-III criteria for major depressive disorder. Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 145 mg/day. Study 2 was a 6-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Overall, these studies demonstrated ZOLOFT to be superior to placebo on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement scales. Study 2 was not readily interpretable regarding a dose response relationship for effectiveness.

Study 3 involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on ZOLOFT 50–200 mg/day. These patients (N=295) were randomized to continuation for 44 weeks on double-blind ZOLOFT 50–200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking ZOLOFT compared to those on placebo. The mean dose for completers was 70 mg/day.

Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex.

The effectiveness of ZOLOFT in the treatment of OCD was demonstrated in three multicenter placebo-controlled studies of adult outpatients (Studies 1–3). Patients in all studies had moderate to severe OCD (DSM-III or DSM-III-R) with mean baseline ratings on the Yale–Brown Obsessive-Compulsive Scale (YBOCS) total score ranging from 23 to 25.

Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 186 mg/day. Patients receiving ZOLOFT experienced a mean reduction of approximately 4 points on the YBOCS total score which was significantly greater than the mean reduction of 2 points in placebo-treated patients.

Study 2 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT doses of 50 and 200 mg/day experienced mean reductions of approximately 6 points on the YBOCS total score which were significantly greater than the approximately 3 point reduction in placebo-treated patients.

Study 3 was a 12-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 185 mg/day. Patients receiving ZOLOFT experienced a mean reduction of approximately 7 points on the YBOCS total score which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

The effectiveness of ZOLOFT for the treatment of OCD was also demonstrated in a 12-week, multicenter, placebo-controlled, parallel group study in a pediatric outpatient population (children and adolescents, ages 6–17). Patients receiving ZOLOFT in this study were initiated at doses of either 25 mg/day (children, ages 6–12) or 50 mg/day (adolescents, ages 13–17), and then titrated over the next four weeks to a maximum dose of 200 mg/day, as tolerated. The mean dose for completers was 178 mg/day. Dosing was once a day in the morning or evening. Patients in this study had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS) total score of 22. Patients receiving sertraline experienced a mean reduction of approximately 7 units on the CYBOCS total score which was significantly greater than the 3 unit reduction for placebo patients. Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

In a longer-term study, patients meeting DSM-III-R criteria for OCD who had responded during a 52-week single-blind trial on ZOLOFT 50–200 mg/day (n=224) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Response during the single-blind phase was defined as a decrease in the YBOCS score of ≥ 25% compared to baseline and a CGI-I of 1 (very much improved), 2 (much improved) or 3 (minimally improved). Relapse during the double-blind phase was defined as the following conditions being met (on three consecutive visits for 1 and 2, and for visit 3 for condition 3): (1) YBOCS score increased by ≥ 5 points, to a minimum of 20, relative to baseline; (2) CGI-I increased by ≥ one point; and (3) worsening of the patient's condition in the investigator's judgment, to justify alternative treatment. Insufficient clinical response indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Patients receiving continued ZOLOFT treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

The effectiveness of ZOLOFT in the treatment of panic disorder was demonstrated in three double-blind, placebo-controlled studies (Studies 1–3) of adult outpatients who had a primary diagnosis of panic disorder (DSM-III-R), with or without agoraphobia.

Studies 1 and 2 were 10-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and then patients were dosed in a range of 50–200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT doses for completers to 10 weeks were 131 mg/day and 144 mg/day, respectively, for Studies 1 and 2. In these studies, ZOLOFT was shown to be significantly more effective than placebo on change from baseline in panic attack frequency and on the Clinical Global Impression Severity of Illness and Global Improvement scores. The difference between ZOLOFT and placebo in reduction from baseline in the number of full panic attacks was approximately 2 panic attacks per week in both studies.

Study 3 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT experienced a significantly greater reduction in panic attack frequency than patients receiving placebo. Study 3 was not readily interpretable regarding a dose response relationship for effectiveness.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age, race, or gender.

In a longer-term study, patients meeting DSM-III-R criteria for Panic Disorder who had responded during a 52-week open trial on ZOLOFT 50–200 mg/day (n=183) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Response during the open phase was defined as a CGI-I score

of 1(very much improved) or 2 (much improved). Relapse during the double-blind phase was defined as the following conditions being met on three consecutive visits: (1) CGI-I ≥ 3; (2) meets DSM-III-R criteria for Panic Disorder; (3) number of panic attacks greater than at baseline. Insufficient clinical response indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Patients receiving continued ZOLOFT treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

The effectiveness of ZOLOFT in the treatment of PTSD was established in two multicenter placebo-controlled studies (Studies 1–2) of adult outpatients who met DSM-III-R criteria for PTSD. The mean duration of PTSD for these patients was 12 years (Studies 1 and 2 combined) and 44% of patients (169 of the 385 patients treated) had secondary depressive disorder.

Studies 1 and 2 were 12-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and patients were then dosed in the range of 50–200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT dose for completers was 146 mg/day and 151 mg/day, respectively for Studies 1 and 2. Study outcome was assessed by the Clinician-Administered PTSD Scale Part 2 (CAPS) which is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of reexperiencing/intrusion, avoidance/numbing, and hyperarousal as well as the patient-rated Impact of Event Scale (IES) which measures intrusion and avoidance symptoms. ZOLOFT was shown to be significantly more effective than placebo on change from baseline to endpoint on the CAPS, IES and on the Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scores. In two additional placebo-controlled PTSD trials, the difference in response to treatment between patients receiving ZOLOFT and patients receiving placebo was not statistically significant. One of these additional studies was conducted in patients similar to those recruited for Studies 1 and 2, while the second additional study was conducted in predominantly male veterans.

As PTSD is a more common disorder in women than men, the majority (76%) of patients in these trials were women (152 and 139 women on sertraline and placebo versus 39 and 55 men on sertraline and placebo; Studies 1 and 2 combined). Post hoc exploratory analyses revealed a significant difference between ZOLOFT and placebo on the CAPS, IES and CGI in women, regardless of baseline diagnosis of comorbid major depressive disorder, but essentially no effect in the relatively smaller number of men in these studies. The clinical significance of this apparent gender interaction is unknown at this time. There was insufficient information to determine the effect of race or age on outcome.

In a longer-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on ZOLOFT 50–200 mg/day (n=96) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for relapse. Response during the open phase was defined as a CGI-I of 1 (very much improved) or 2 (much improved), and a decrease in the CAPS-2 score of > 30% compared to baseline. Relapse during the double-blind phase was defined as the following conditions being met on two consecutive visits: (1) CGI-I ≥ 3; (2) CAPS-2 score increased by ≥ 30% and by ≥ 15 points relative to baseline; and (3) worsening of the patient's condition in the investigator's judgment. Patients receiving continued ZOLOFT treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

The effectiveness of ZOLOFT for the treatment of PMDD was established in two double-blind, parallel group, placebo-controlled flexible dose trials (Studies 1 and 2) conducted over 3 menstrual cycles. Patients in Study 1 met DSM-III-R criteria for Late Luteal Phase Dysphoric Disorder (LLPDD), the clinical entity now referred to as Premenstrual Dysphoric Disorder (PMDD) in DSM-IV. Patients in Study 2 met DSM-IV criteria for PMDD. Study 1 utilized daily dosing throughout the study, while Study 2 utilized luteal phase dosing for the 2 weeks prior to the onset of menses. The mean duration of PMDD

symptoms for these patients was approximately 10.5 years in both studies. Patients on oral contraceptives were excluded from these trials; therefore, the efficacy of sertraline in combination with oral contraceptives for the treatment of PMDD is unknown.

Efficacy was assessed with the Daily Record of Severity of Problems (DRSP), a patient-rated instrument that mirrors the diagnostic criteria for PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms, and other symptoms. Other efficacy assessments included the Hamilton Depression Rating Scale (HAMD-17), and the Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I) scores.

In Study 1, involving n=251 randomized patients; ZOLOFT treatment was initiated at 50 mg/day and administered daily throughout the menstrual cycle. In subsequent cycles, patients were dosed in the range of 50–150 mg/day on the basis of clinical response and toleration. The mean dose for completers was 102 mg/day. ZOLOFT administered daily throughout the menstrual cycle was significantly more effective than placebo on change from baseline to endpoint on the DRSP total score, the HAMD-17 total score, and the CGI-S score, as well as the CGI-I score at endpoint.

In Study 2, involving n=281 randomized patients, ZOLOFT treatment was initiated at 50 mg/day in the late luteal phase (last 2 weeks) of each menstrual cycle and then discontinued at the onset of menses. In subsequent cycles, patients were dosed in the range of 50–100 mg/day in the luteal phase of each cycle, on the basis of clinical response and toleration. Patients who were titrated to 100 mg/day received 50 mg/day for the first 3 days of the cycle, then 100 mg/day for the remainder of the cycle. The mean ZOLOFT dose for completers was 74 mg/day. ZOLOFT administered in the late luteal phase of the menstrual cycle was significantly more effective than placebo on change from baseline to endpoint on the DRSP total score and the CGI-S score, as well as the CGI-I score at endpoint.

There was insufficient information to determine the effect of race or age on outcome in these studies.

The effectiveness of ZOLOFT in the treatment of social anxiety disorder (also known as social phobia) was established in two multicenter placebo-controlled studies (Study 1 and 2) of adult outpatients who met DSM-IV criteria for social anxiety disorder.

Study 1 was a 12-week, multicenter, flexible dose study comparing ZOLOFT (50–200 mg/day) to placebo, in which ZOLOFT was initiated at 25 mg/day for the first week. Study outcome was assessed by (a) the Liebowitz Social Anxiety Scale (LSAS), a 24-item clinician administered instrument that measures fear, anxiety and avoidance of social and performance situations, and by (b) the proportion of responders as defined by the Clinical Global Impression of Improvement (CGI-I) criterion of CGI-I ≤ 2 (very much or much improved). ZOLOFT was statistically significantly more effective than placebo as measured by the LSAS and the percentage of responders.

Study 2 was a 20-week, multicenter, flexible dose study that compared ZOLOFT (50–200 mg/day) to placebo. Study outcome was assessed by the (a) Duke Brief Social Phobia Scale (BSPS), a multi-item clinician-rated instrument that measures fear, avoidance and physiologic response to social or performance situations, (b) the Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS), a 5-item patient-rated instrument that measures change in the severity of phobic avoidance and distress, and (c) the CGI-I responder criterion of ≤ 2. ZOLOFT was shown to be statistically significantly more effective than placebo as measured by the BSPS total score and fear, avoidance and physiologic factor scores, as well as the FQ-SPS total score, and to have significantly more responders than placebo as defined by the CGI-I.

Subgroup analyses did not suggest differences in treatment outcome on the basis of gender. There was insufficient information to determine the effect of race or age on outcome.

In a longer-term study, patients meeting DSM-IV criteria for social anxiety disorder who had responded while assigned to ZOLOFT (CGI-I of 1 or 2) during a 20-week placebo-controlled trial on ZOLOFT 50–200 mg/day were randomized to continuation of ZOLOFT or to substitution of placebo for up to 24

weeks of observation for relapse. Relapse was defined as ≥ 2 point increase in the Clinical Global Impression – Severity of Illness (CGI-S) score compared to baseline or study discontinuation due to lack of efficacy. Patients receiving ZOLOFT continuation treatment experienced a statistically significantly lower relapse rate over this 24-week study than patients randomized to placebo substitution.

INDICATIONS & USAGE

ZOLOFT (sertraline hydrochloride) is indicated for the treatment of major depressive disorder in adults.

The efficacy of ZOLOFT in the treatment of a major depressive episode was established in six to eight week controlled trials of adult outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of ZOLOFT in hospitalized depressed patients has not been adequately studied.

The efficacy of ZOLOFT in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving ZOLOFT for extended periods should be reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).

ZOLOFT is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of ZOLOFT was established in 12-week trials with obsessive-compulsive outpatients having diagnoses of obsessive-compulsive disorder as defined according to DSM-III or DSM-III-R criteria (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The efficacy of ZOLOFT in maintaining a response, in patients with OCD who responded during a 52-week treatment phase while taking ZOLOFT and were then observed for relapse during a period of up to 28 weeks, was demonstrated in a placebo-controlled trial (see Clinical Trials under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

ZOLOFT is indicated for the treatment of panic disorder in adults, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of ZOLOFT was established in three 10–12 week trials in adult panic disorder patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The efficacy of ZOLOFT in maintaining a response, in adult patients with panic disorder who responded during a 52-week treatment phase while taking ZOLOFT and were then observed for relapse during a period of up to 28 weeks, was demonstrated in a placebo-controlled trial (see Clinical Trials under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

ZOLOFT (sertraline hydrochloride) is indicated for the treatment of posttraumatic stress disorder in adults.

The efficacy of ZOLOFT in the treatment of PTSD was established in two 12-week placebo-controlled trials of adult outpatients whose diagnosis met criteria for the DSM-III-R category of PTSD (see Clinical Trials under CLINICAL PHARMACOLOGY).

PTSD, as defined by DSM-III-R/IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of ZOLOFT in maintaining a response in adult patients with PTSD for up to 28 weeks following 24 weeks of open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

ZOLOFT is indicated for the treatment of premenstrual dysphoric disorder (PMDD) in adults.

The efficacy of ZOLOFT in the treatment of PMDD was established in 2 placebo-controlled trials of female adult outpatients treated for 3 menstrual cycles who met criteria for the DSM-III-R/IV category of PMDD (see Clinical Trials under CLINICAL PHARMACOLOGY).

The essential features of PMDD include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical

symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of ZOLOFT in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

ZOLOFT (sertraline hydrochloride) is indicated for the treatment of social anxiety disorder, also known as social phobia in adults.

The efficacy of ZOLOFT in the treatment of social anxiety disorder was established in two placebo-controlled trials of adult outpatients with a diagnosis of social anxiety disorder as defined by DSM-IV criteria (see Clinical Trials under CLINICAL PHARMACOLOGY).

Social anxiety disorder, as defined by DSM-IV, is characterized by marked and persistent fear of social or performance situations involving exposure to unfamiliar people or possible scrutiny by others and by fears of acting in a humiliating or embarrassing way. Exposure to the feared social situation almost always provokes anxiety and feared social or performance situations are avoided or else are endured with intense anxiety or distress. In addition, patients recognize that the fear is excessive or unreasonable and the avoidance and anticipatory anxiety of the feared situation is associated with functional impairment or marked distress.

The efficacy of ZOLOFT in maintaining a response in adult patients with social anxiety disorder for up to 24 weeks following 20 weeks of ZOLOFT treatment was demonstrated in a placebo-controlled trial. Physicians who prescribe ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Clinical Trials under CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

The use of MAOIs intended to treat psychiatric disorders with ZOLOFT or within 14 days of stopping treatment with ZOLOFT is contraindicated because of an increased risk of serotonin syndrome. The use of ZOLOFT within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (see WARNINGS and DOSAGE AND ADMINISTRATION).

Starting ZOLOFT 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 (see WARNINGS and DOSAGE AND ADMINISTRATION).

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

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

ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

WARNINGS

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 (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with ZOLOFT, for a description of the risks of discontinuation of ZOLOFT).

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 ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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 ZOLOFT is not approved for use in treating bipolar depression.

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including ZOLOFT, 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 ZOLOFT with MAOIs intended to treat psychiatric disorders is contraindicated. ZOLOFT 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 ZOLOFT. ZOLOFT should be discontinued before initiating treatment with the MAOI (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

If concomitant use of ZOLOFT 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 ZOLOFT and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

PRECAUTIONS

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

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.

ZOLOFT 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 ZOLOFT 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, ZOLOFT should be introduced with care in patients with a seizure disorder.

During marketing of ZOLOFT 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 ZOLOFT. 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).

SSRIs and SNRIs, including ZOLOFT, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants 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. 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 ZOLOFT and NSAIDs, aspirin, or other drugs that affect coagulation.

ZOLOFT (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.

Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT 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 ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities.

ZOLOFT 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. ZOLOFT 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).

ZOLOFT is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, Cmax 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 (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Since ZOLOFT 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 (see CLINICAL PHARMACOLOGY).

In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance (See **Information for Patients**).

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including ZOLOFT. 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 (see GERIATRIC USE).

Discontinuation of ZOLOFT 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.

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

SSRIs including sertraline may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. Sertraline should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with ZOLOFT 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 ZOLOFT. 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 ZOLOFT.

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 ZOLOFT, and triptans, tramadol, or other serotonergic agents.

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

Patients should be told that while no adverse interaction of ZOLOFT 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.

ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for persons with latex sensitivity, as the dropper dispenser contains dry natural rubber.

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.

Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT (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 ZOLOFT 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 ZOLOFT (50–200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.

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

In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT 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 ZOLOFT 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 ZOLOFT 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 ZOLOFT 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 Cmax 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 ZOLOFT and pimozide should be contraindicated (see CONTRAINDICATIONS).

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 ZOLOFT 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 ZOLOFT 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 ZOLOFT therapy with appropriate adjustments to the valproate dose.

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

See CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION.

In three separate *in vivo* interaction studies, sertraline was co-administered 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 Cmax were reduced by about 35%).

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 ZOLOFT may require lower doses than usually prescribed for the other drug. Furthermore, whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the co-administered drug may be required (see Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder under PRECAUTIONS).

See CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION.

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 ZOLOFT, with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS – Serotonin Syndrome).

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.

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 ZOLOFT, 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 ZOLOFT (see Drugs Metabolized by P450 2D6 under PRECAUTIONS).

In a placebo-controlled trial in normal volunteers, administration of ZOLOFT 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. ZOLOFT 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.

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

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

Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies, ZOLOFT 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.

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. These studies 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 ZOLOFT is initiated or discontinued.

There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT.

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

Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10–40 mg/kg (0.25–1.0 times the MRHD on a mg/m^2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10–40 mg/kg (0.5–2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related.

Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.

A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).

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. ZOLOFT (sertraline hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Neonates exposed to ZOLOFT 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 (see WARNINGS: 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 ZOLOFT) 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 ZOLOFT, 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 (see DOSAGE AND ADMINISTRATION).

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

It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.

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

The safety of ZOLOFT 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. ZOLOFT 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, ZOLOFT 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 weight (see Pharmacokinetics under CLINICAL PHARMACOLOGY).

Approximately 600 patients with major depressive disorder or OCD between 6 and 17 years of age have received ZOLOFT 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 ZOLOFT (see ADVERSE REACTIONS). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. 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 ZOLOFT's 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 (see **WARNINGS – Clinical Worsening and Suicide Risk**).

U.S. geriatric clinical studies of ZOLOFT in major depressive disorder included 663 ZOLOFT-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 subjects (see ADVERSE REACTIONS), 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 ZOLOFT 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 ZOLOFT 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 ZOLOFT, 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).

ADVERSE REACTIONS

During its premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects as of February 18, 2000. The conditions and duration of exposure to ZOLOFT 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 ZOLOFT who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving ZOLOFT. 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.

Table 2 enumerates the most common treatment-emergent adverse events associated with the use of ZOLOFT (incidence of at least 5% for ZOLOFT 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[1], OCD, panic disorder, PTSD, PMDD and social anxiety disorder in placebo-controlled clinical trials. Most patients in major depressive disorder/other[1], 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 ZOLOFT and with incidence greater than placebo who participated in controlled clinical trials comparing ZOLOFT with placebo in the treatment of major depressive disorder/other[1], 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	**ZOLOFT (N=861)**	**Placebo (N=853)**	**ZOLOFT (N=533)**	**Placebo (N=373)**	**ZOLOFT (N=430)**	**Placebo (N=275)**	**ZOLOFT (N=374)**	**Placebo (N=376)**
Autonomic Nervous System Disorders								
Ejaculation Failure†	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 Anxiety Disorder**			
Body System/Adverse Event	**ZOLOFT (N=121)**	**Placebo (N=122)**	**ZOLOFT (N=136)**	**Placebo (N=127)**	**ZOLOFT (N=344)**	**Placebo (N=268)**

Autonomic Nervous System Disorders						
Ejaculation Failure[2]	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

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†	**ZOLOFT (N=2799)**	**Placebo (N=2394)**
Autonomic Nervous System Disorders		
Ejaculation Failure‡	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

Table 4 lists the adverse events associated with discontinuation of ZOLOFT (sertraline hydrochloride) treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT in clinical trials) in major depressive disorder/other[7], 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[7] (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%	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%	–	–	–	–	–	–

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 ZOLOFT in placebo-controlled trials.

TABLE 5

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

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.

In over 600 pediatric patients treated with ZOLOFT, 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 ZOLOFT): fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis and purpura.

Following is a list of treatment-emergent adverse events reported during premarketing assessment of ZOLOFT 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 ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. 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 ZOLOFT treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, 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, 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.

In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT (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.

ZOLOFT 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 ZOLOFT treatment in patients with major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder is similar.

Reports of adverse events temporally associated with ZOLOFT 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-type 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 ZOLOFT) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

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1 Major depressive disorder and other premarketing controlled trials.

2 Primarily ejaculatory delay. Denominator used was for male patients only (N=271 ZOLOFT major depressive disorder/other*; N=271 placebo major depressive disorder/other*; N=296 ZOLOFT OCD; N=219 placebo OCD; N=216 ZOLOFT panic disorder; N=134 placebo panic disorder; N=130 ZOLOFT PTSD; N=149 placebo PTSD; No male patients in PMDD studies; N=205 ZOLOFT social anxiety disorder; N=153 placebo social anxiety disorder).

3 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.

4 Major depressive disorder and other premarketing controlled trials.

[5] Included are events reported by at least 2% of patients taking ZOLOFT except the following events, which had an incidence on placebo greater than or equal to ZOLOFT: abdominal pain, back pain, flatulence, malaise, pain, pharyngitis, respiratory disorder, upper respiratory tract infection.

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

[7] Major depressive disorder and other premarketing controlled trials.

[8] 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).

[9] Denominator used was for male patients only (N=1118 ZOLOFT; N=926 placebo)

[10] Denominator used was for male and female patients (N=2799 ZOLOFT; N=2394 placebo)

DRUG ABUSE AND DEPENDENCE

ZOLOFT (sertraline hydrochloride) is not a controlled substance.

In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of ZOLOFT, alprazolam, and d-amphetamine in humans, ZOLOFT 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 ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. In animal studies ZOLOFT 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 ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

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 and syncope.

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. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference*® (PDR®).

DOSAGE & ADMINISTRATION

ZOLOFT treatment should be administered at a dose of 50 mg once daily.

ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily.

While a relationship between dose and effect has not been established for major depressive disorder, OCD, panic disorder, PTSD or social anxiety disorder, patients were dosed in a range of 50–200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

ZOLOFT treatment should be initiated with a dose of 50 mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.

While a relationship between dose and effect has not been established for PMDD, patients were dosed in the range of 50–150 mg/day with dose increases at the onset of each new menstrual cycle (see Clinical Trials under CLINICAL PHARMACOLOGY). Patients not responding to a 50 mg/day dose may benefit from dose increases (at 50 mg increments/menstrual cycle) up to 150 mg/day when dosing daily throughout the menstrual cycle, or 100 mg/day when dosing during the luteal phase of the menstrual cycle. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilized at the beginning of each luteal phase dosing period.

ZOLOFT should be administered once daily, either in the morning or evening.

ZOLOFT treatment should be initiated with a dose of 25 mg once daily in children (ages 6–12) and at a dose of 50 mg once daily in adolescents (ages 13–17).

While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25–200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for pediatric patients (6–17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

ZOLOFT should be administered once daily, either in the morning or evening.

It is generally agreed that acute episodes of major depressive disorder require several months or

longer of sustained pharmacologic therapy beyond response to the acute episode. Systematic evaluation of ZOLOFT has demonstrated that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of initial treatment at a dose of 50–200 mg/day (mean dose of 70 mg/day) (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of ZOLOFT has demonstrated that its efficacy in PTSD is maintained for periods of up to 28 weeks following 24 weeks of treatment at a dose of 50–200 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Social anxiety disorder is a chronic condition that may require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of ZOLOFT has demonstrated that its efficacy in social anxiety disorder is maintained for periods of up to 24 weeks following 20 weeks of treatment at a dose of 50–200 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). Dosage adjustments should be made to maintain patients on the lowest effective dose and patients should be periodically reassessed to determine the need for long-term treatment.

It is generally agreed that OCD and Panic Disorder require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of continuing ZOLOFT for periods of up to 28 weeks in patients with OCD and Panic Disorder who have responded while taking ZOLOFT during initial treatment phases of 24 to 52 weeks of treatment at a dose range of 50–200 mg/day has demonstrated a benefit of such maintenance treatment (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

The effectiveness of ZOLOFT in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. However, as women commonly report that symptoms worsen with age until relieved by the onset of menopause, it is reasonable to consider continuation of a responding patient. Dosage adjustments, which may include changes between dosage regimens (e.g., daily throughout the menstrual cycle versus during the luteal phase of the menstrual cycle), may be needed to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with ZOLOFT. Conversely, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI intended to treat psychiatric disorders (see CONTRAINDICATIONS).

Do not start ZOLOFT in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered (see

CONTRAINDICATIONS).

In some cases, a patient already receiving ZOLOFT therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, ZOLOFT should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with ZOLOFT may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see WARNINGS).

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with ZOLOFT is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see WARNINGS).

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 (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Neonates exposed to ZOLOFT 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 ZOLOFT during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Symptoms associated with discontinuation of ZOLOFT 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.

ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for patients with latex sensitivity, as the dropper dispenser contains dry natural rubber.

ZOLOFT Oral Concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

HOW SUPPLIED

ZOLOFT (sertraline hydrochloride) capsular-shaped scored tablets, containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline, are packaged in bottles.

ZOLOFT 25 mg Tablets: light green film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 25 mg.

NDC 0049-4960-30	Bottles of 30
NDC 0049-4960-50	Bottles of 50

ZOLOFT 50 mg Tablets: light blue film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 50 mg.

NDC 0049-4900-30	Bottles of 30
NDC 0049-4900-66	Bottles of 100
NDC 0049-4900-73	Bottles of 500
NDC 0049-4900-94	Bottles of 5000
NDC 0049-4900-41	Unit Dose Packages of 100

ZOLOFT 100 mg Tablets: light yellow film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 100 mg.

NDC 0049-4910-30	Bottles of 30
NDC 0049-4910-66	Bottles of 100
NDC 0049-4910-73	Bottles of 500
NDC 0049-4910-94	Bottles of 5000
NDC 0049-4910-41	Unit Dose Packages of 100

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

ZOLOFT Oral Concentrate: ZOLOFT Oral Concentrate is a clear, colorless solution with a menthol scent containing sertraline hydrochloride equivalent to 20 mg of sertraline per mL and 12% alcohol. It is supplied as a 60 mL bottle with an accompanying calibrated dropper.

NDC 0049-4940-23	Bottles of 60 mL

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

SPL UNCLASSIFIED

Rx only

LAB-0218-27.0

December 2012

SPL MEDGUIDE

ZOLOFT (ZOH-loft)
(sertraline hydrochloride)
(Tablets and Oral Concentrate (solution))

Read the Medication Guide that comes with ZOLOFT before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about ZOLOFT?

ZOLOFT and other antidepressant medicines may cause serious side effects, including:
1.**Suicidal thoughts or actions:**

- **ZOLOFT and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
  - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
  - Pay particular attention to such changes when ZOLOFT is started or when the dose is changed.

  Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.
  Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:
  - attempts to commit suicide
  - acting on dangerous impulses
  - acting aggressive or violent
  - thoughts about suicide or dying
  - new or worse depression
  - new or worse anxiety or panic attacks
  - feeling agitated, restless, angry or irritable
  - trouble sleeping
  - an increase in activity or talking more than what is normal for you
  - other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. ZOLOFT may be associated with these serious side effects:2.**Serotonin Syndrome This condition can be life-threatening and may include**:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle rigidity

3.**Severe allergic reactions:**

- trouble breathing
- swelling of the face, tongue, eyes or mouth
- rash, itchy welts (hives) or blisters, alone or with fever or joint pain

4.**Abnormal bleeding**: ZOLOFT and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.5.**Seizures or convulsions**
6.**Manic episodes:**

- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

7.**Changes in appetite or weight.** Children and adolescents should have height and weight monitored during treatment.8.**Low salt (sodium) levels in the blood.** Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

Do not stop ZOLOFT without first talking to your healthcare provider. Stopping ZOLOFT too quickly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or changes in sleep habits
- headache, sweating, nausea, dizziness
- electric shock-like sensations, shaking, confusion

What is ZOLOFT?

ZOLOFT is a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider. ZOLOFT is also used to treat:

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Panic Disorder
- Posttraumatic Stress Disorder (PTSD)
- Social Anxiety Disorder
- Premenstrual Dysphoric Disorder (PMDD)

Talk to your healthcare provider if you do not think that your condition is getting better with ZOLOFT treatment.

Who should not take ZOLOFT?

Do not take ZOLOFT if you:

- are allergic to sertraline or any of the ingredients in ZOLOFT. See the end of this Medication Guide for a complete list of ingredients in ZOLOFT.
- **take the antipsychotic medicine pimozide (Orap®) because this can cause serious heart problems.**
- take Antabuse® (disulfiram) (if you are taking the liquid form of ZOLOFT) due to the alcohol content.
- take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI within 2 weeks of stopping ZOLOFT unless directed to do so by your physician.
- Do not start ZOLOFT if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.
  People who take ZOLOFT close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:
  - high fever
  - uncontrolled muscle spasms
  - stiff muscles
  - rapid changes in heart rate or blood pressure
  - confusion
  - loss of consciousness (pass out)

What should I tell my healthcare provider before taking ZOLOFT? Ask if you are not sure.

Before starting ZOLOFT, tell your healthcare provider if you:

- Are taking certain drugs such as:
  - Medicines used to treat migraine headaches such as:
    - triptans
  - Medicines used to treat mood, anxiety, psychotic or thought disorders, such as:
    - tricyclic antidepressants
    - lithium
    - diazepam
    - SSRIs
    - SNRIs
    - antipsychotic drugs
    - valproate
  - Medicines used to treat seizures such as:
    - phenytoin
  - Medicines used to treat pain such as:
    - tramadol
  - Medicines used to thin your blood such as:
    - warfarin
  - Medicines used to control your heartbeat such as :
    - propafenone
    - flecainide
    - digitoxin
  - Medicines used to treat type II diabetes such as:
    - tolbutamide

    - Cimetidine used to treat heartburn
    - Over-the-counter medicines or supplements such as:
        - Aspirin or other NSAIDs
        - tryptophan
        - St. John's Wort
- have liver problems
- have kidney problems.
- have heart problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have a history of a stroke
- have high blood pressure
- have or had bleeding problems
- are pregnant or plan to become pregnant. It is not known if ZOLOFT will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy.
- are breast-feeding or plan to breast-feed. Some ZOLOFT may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking ZOLOFT.

Tell your healthcare provider about all the medicines **that you take,** including prescription and non-prescription medicines, vitamins, and herbal supplements. ZOLOFT and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take ZOLOFT with your other medicines. Do not start or stop any medicine while taking ZOLOFT without talking to your healthcare provider first.

If you take ZOLOFT, you should not take any other medicines that contain sertraline (sertraline HCl, sertraline hydrochloride, etc.).

How should I take ZOLOFT?

- Take ZOLOFT exactly as prescribed. Your healthcare provider may need to change the dose of ZOLOFT until it is the right dose for you.
- ZOLOFT Tablets may be taken with or without food.
- ZOLOFT Oral Concentrate must be diluted before use:
    - Follow the instructions carefully
    - When diluting ZOLOFT Oral Concentrate, use ONLY water, ginger ale, lemon/lime soda, lemonade, or orange juice.
    - If you are sensitive to latex, be careful when using the dropper to dispense the Oral Concentrate.
- If you miss a dose of ZOLOFT, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of ZOLOFT at the same time.
- If you take too much ZOLOFT, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking ZOLOFT?

ZOLOFT can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how ZOLOFT affects you. Do not drink alcohol while using ZOLOFT.

What are the possible side effects of ZOLOFT?

ZOLOFT may cause serious side effects, including:

- See "What is the most important information I should know about ZOLOFT?"
- **Feeling anxious or trouble sleeping**

Common possible side effects in people who take ZOLOFT include:

- nausea, loss of appetite, diarrhea or indigestion
- change in sleep habits including increased sleepiness or insomnia
- increased sweating
- sexual problems including decreased libido and ejaculation failure
- tremor or shaking
- feeling tired or fatigued
- agitation

Other side effects in children and adolescents include:

- abnormal increase in muscle movement or agitation
- nose bleed
- urinating more often
- urinary incontinence
- aggressive reaction
- heavy menstrual periods
- possible slowed growth rate and weight change. Your child's height and weight should be monitored during treatment with ZOLOFT.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ZOLOFT. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store ZOLOFT?

- Store ZOLOFT at room temperature, between 59°F and 86°F (15°C to 30°C).
- Keep ZOLOFT bottle closed tightly.

Keep ZOLOFT and all medicines out of the reach of children.

General information about ZOLOFT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZOLOFT for a condition for which it was not prescribed. Do not give ZOLOFT to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about ZOLOFT. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about ZOLOFT that is written for healthcare professionals.

For more information about ZOLOFT call 1-800-438-1985 or go to www.pfizer.com

What are the ingredients in ZOLOFT?

Active ingredient: sertraline hydrochloride

Inactive ingredients

- **Tablets:** dibasic calcium phosphate dihydrate, D&C Yellow #10 aluminum lake (in 25 mg tablet), FD&C Blue #1 aluminum lake (in 25 mg tablet), FD&C Red #40 aluminum lake (in 25 mg tablet), FD&C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate,

synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide

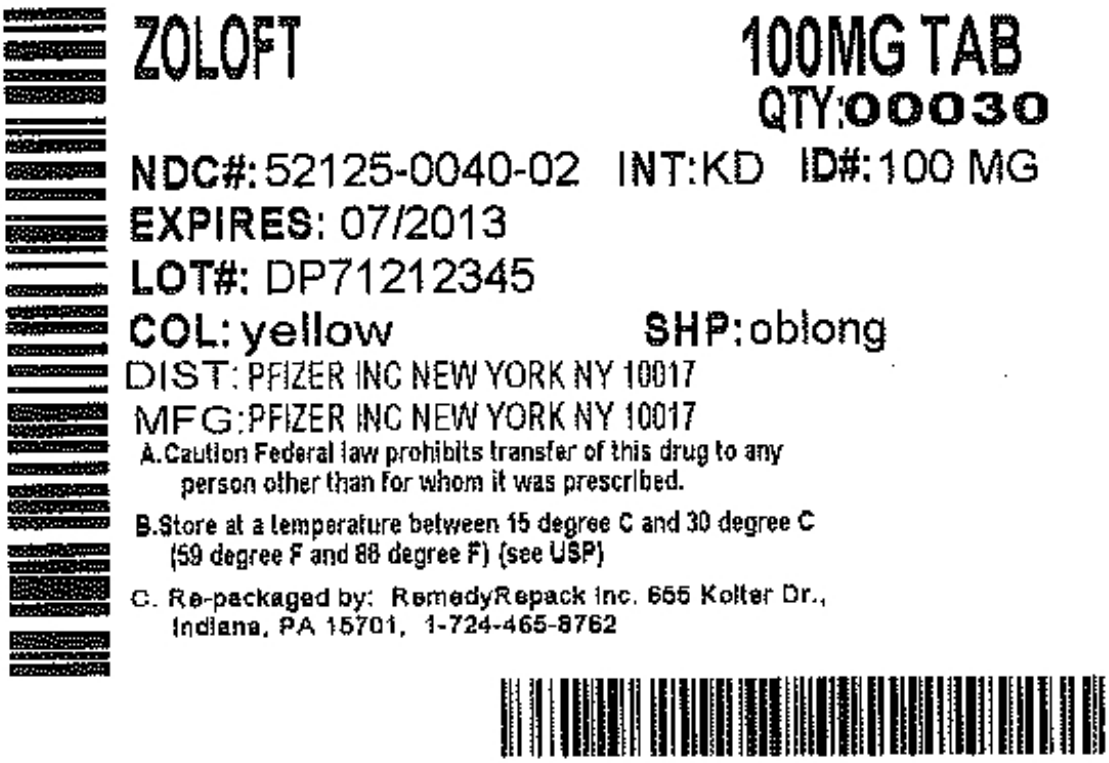
- **Oral concentration:** glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT)

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

LAB-0540-3.0

December 2012

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL SECTION
DRUG: Zoloft
GENERIC: SERTRALINE HYDROCHLORIDE
DOSAGE: TABLET, FILM COATED
ADMINSTRATION: ORAL
NDC: 52125-040-02
STRENGTH:100 mg
COLOR: yellow
SHAPE: CAPSULE
SCORE: Two even pieces
SIZE: 13 mm
IMPRINT: 30
QTY: 30



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ZOLOFT

sertraline hydrochloride tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:52125-040(NDC:0049-4910)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SERTRALINE HYDROCHLORIDE (SERTRALINE)	SERTRALINE	100 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM PHOSPHATE, DIBASIC, DIHYDRATE	
D&C YELLOW NO. 10	
FD&C BLUE NO. 1	
FD&C RED NO. 40	
HYDROXYPROPYL CELLULOSE (TYPE H)	
HYPROMELLOSES	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
POLYETHYLENE GLYCOLS	
POLYSORBATE 80	
TITANIUM DIOXIDE	
ALUMINUM OXIDE	
FD&C BLUE NO. 2	
FERRIC OXIDE YELLOW	
GLYCERIN	
ALCOHOL, X-RAY EXPOSED (1000 RAD)	
MENTHOL 1-PROPYLENE GLYCOL CARBONATE, (-)-	
BUTYLATED HYDROXYTOLUENE	

Product Characteristics

Color	yellow	**Score**	2 pieces
Shape	CAPSULE (TABLET, FILM COATED)	**Size**	13mm
Flavor		**Imprint Code**	ZOLOFT;100;mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52125-040-02	30 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019839	02/25/2013	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 2/2013 REMEDYREPACK INC.