

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 1

[Note: Below is the Agency's final labeling for Zoloft tablets and oral concentrate for the long-term safety of Zoloft in the treatment of pediatric obsessive compulsive disorder (OCD). This labeling is identical to the most recently approved labeling for Zoloft (approved in an Agency letter dated September 19, 2001) except for the highlighted revisions. This labeling represents the agreed upon labeling changes as submitted in your April 20, 2001 resubmission along with the labeling changes requested in our letter dated September 19, 2001. Double underline font denotes additions to the labeling, and strikeout font denotes deletions to the labeling.]

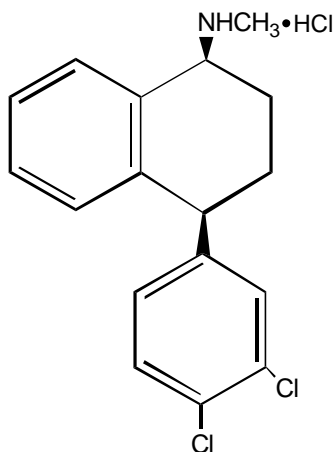
ZOLOFT[®]

(sertraline hydrochloride)

Tablets and Oral Concentrate

DESCRIPTION

ZOLOFT[®] (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. ~~It is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents.~~ 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 $C_{17}H_{17}NCl_2 \cdot HCl$ 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, hydroxypropyl methylcellulose, magnesium stearate,

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 2

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

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (α_1 , α_2 , β), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5HT_{1A}, 5HT_{1B}, 5HT₂), 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 downregulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

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

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

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

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 3

oral concentrate, T_{max} was slightly prolonged from 5.9 hours to 7.0 hours with food.

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

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

Protein Binding—*In vitro* protein binding studies performed with radiolabeled ³H-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).

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

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

Liver Disease—As might be predicted from its primary site of metabolism, liver impairment can

NDA 19-839/S-033 & 20-990/S-001

Approved Labeling Enclosure

Page 4

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).

Renal Disease—Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CL_{Cr}=30-60 mL/min), moderate to severe (CL_{Cr}=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).

Clinical Trials

Major Depressive Disorder—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.

Obsessive-Compulsive Disorder (OCD)—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.

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 5

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~~ [points](#) on the CYBOCS total score which was significantly greater than the 3 ~~unit~~ [point](#) 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.

Panic Disorder—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.

NDA 19-839/S-033 & 20-990/S-001

Approved Labeling Enclosure

Page 6

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

Posttraumatic Stress Disorder (PTSD)—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 \geq 3; (2) CAPS-2 score increased by \geq 30% and by \geq 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.

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 7

INDICATIONS AND USAGE

Major Depressive Disorder—ZOLOFT[®] (sertraline hydrochloride) is indicated for the treatment of major depressive disorder.

The efficacy of ZOLOFT in the treatment of a major depressive episode was established in six to eight week controlled trials of 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).

Obsessive-Compulsive Disorder—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 effectiveness of ZOLOFT in long-term use for OCD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use ZOLOFT for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder—ZOLOFT is indicated for the treatment of panic disorder, 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 panic disorder patients

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 8

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 effectiveness of ZOLOFT[®] (sertraline hydrochloride) in long-term use, that is, for more than 12 weeks, 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).

Posttraumatic Stress Disorder (PTSD)—ZOLOFT (sertraline hydrochloride) is indicated for the treatment of posttraumatic stress disorder.

The efficacy of ZOLOFT in the treatment of PTSD was established in two 12-week placebo-controlled trials of 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 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 Clinical Trials under CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

All Dosage Forms of ZOLOFT:

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

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 9

WARNINGS).

Oral Concentrate:

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

WARNINGS

Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT[®] (sertraline hydrochloride), a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.

PRECAUTIONS

General

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT[®] (sertraline hydrochloride) treated patients.

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

Seizure—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.

Suicide—The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. 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.

Because of the well-established comorbidity between OCD and major depressive disorder, panic disorder and major depressive disorder, and PTSD and major depressive disorder, the same

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 10

precautions observed when treating patients with major depressive disorder should be observed when treating patients with OCD, panic disorder or PTSD.

Weak Uricosuric Effect—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.

Use in Patients with Concomitant Illness—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.

ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses 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 is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, C_{max} and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (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).

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

Hyponatremia—Several cases of hyponatremia have been reported and appeared to be reversible when ZOLOFT was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Platelet Function—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.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT:

NDA 19-839/S-033 & 20-990/S-001

Approved Labeling Enclosure

Page 11

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 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.

Laboratory Tests

None.

Drug Interactions

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—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.

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 12

Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.

Cimetidine—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%), C_{max} (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

CNS Active Drugs—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 T_{max} 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.

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, and posttraumatic stress 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.

Monoamine Oxidase Inhibitors—See CONTRAINDICATIONS and WARNINGS.

Drugs Metabolized by P450 3A4—In two separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline co-administration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance.

Drugs Metabolized by P450 2D6—Many drugs effective in the treatment of major depressive disorder, e.g., the SSRIs, including sertraline, and most tricyclic antidepressant drugs effective in the treatment of major depressive disorder inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressant drugs effective in the treatment of major depressive disorder and the Type 1C antiarrhythmics propafenone and flecainide. The extent to

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 13

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).

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

Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)—The extent to which SSRI–TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with 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).

Hypoglycemic Drugs—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.

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

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

Microsomal Enzyme Induction—Preclinical studies have shown 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.

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

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 14

Alcohol—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.

Carcinogenesis—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/m² 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/m² 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/m² 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/m² basis) compared to placebo controls, this effect was not clearly drug related.

Mutagenesis—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.

Impairment of Fertility—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/m² basis).

Pregnancy—Pregnancy Category C—Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m² 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/m² basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m² 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/m² basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m² 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.

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

Nursing Mothers—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.

Pediatric Use—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

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 15

(see Clinical Trials under CLINICAL PHARMACOLOGY). The ~~effectiveness~~ efficacy of ZOLOFT in pediatric patients with major depressive disorder, ~~or~~ panic disorder or PTSD has not been systematically evaluated.

The safety of ZOLOFT use in children and adolescents, 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~~ 18 years of age with major depressive disorder and/or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see Pharmacokinetics under CLINICAL PHARMACOLOGY).

More than 250 patients with major depressive disorder and/or OCD between 6 and ~~17~~ 18 years of age have received ZOLOFT in clinical trials. 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. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.

~~The risks, if any, that may be associated with sertraline's extended use in children and adolescents with OCD have not been systematically assessed.~~ The risks, if any, that may be associated with Zoloft's use beyond 1 year in children and adolescents with OCD 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 ~~relatively short-term~~ clinical studies that were 12 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.

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 16

Geriatric Use—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 1 and 2. Urinary tract infection was the only adverse event not appearing in Tables 1 and 2 and reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials.

As with other SSRIs, ZOLOFT has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under PRECAUTIONS).

ADVERSE REACTIONS

During its premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects as of February 26, 1998. 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 and PTSD.

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.

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 17

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 nondrug factors to the side effect incidence rate in the population studied.

Incidence in Placebo-Controlled Trials—Table 1 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*, OCD, panic disorder and PTSD in placebo-controlled clinical trials. Most patients received doses of 50 to 200 mg/day. Table 2 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*, OCD, panic disorder and PTSD. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 18

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN
PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/Adverse Event	Percentage of Patients Reporting Event							
	Major Depressive Disorder/Other*		OCD		Panic Disorder		PTSD	
	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 ⁽¹⁾	7	<1	17	2	19	1	11	1
Mouth Dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Centr. & Periph. Nerv. System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
General								
Fatigue	11	8	14	10	11	6	10	5
Gastrointestinal Disorders								
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

⁽¹⁾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).

*Major depressive disorder and other premarketing controlled trials.

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 19

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN
PLACEBO-CONTROLLED CLINICAL TRIALS
Percentage of Patients Reporting Event
Major Depressive Disorder/Other*, OCD, Panic Disorder and PTSD combined

Body System/Adverse Event**	ZOLOFT (N=2198)	Placebo (N=1877)
Autonomic Nervous System Disorders		
Ejaculation Failure ⁽¹⁾	14	1
Mouth Dry	15	9
Sweating Increased	6	2
Centr. & Periph. Nerv. System Disorders		
Somnolence	14	7
Dizziness	12	7
Headache	26	24
Paresthesia	3	2
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	7	5
Diarrhea/Loose Stools	21	11
Dyspepsia	8	4
Flatulence	4	3
Nausea	27	13
Vomiting	4	2
General		
Fatigue	11	7
Hot Flushes	2	1
Psychiatric Disorders		
Agitation	6	4
Anxiety	4	3
Insomnia	22	11
Libido Decreased	6	1
Nervousness	6	4
Special Senses		
Vision Abnormal	4	2

⁽¹⁾Primarily ejaculatory delay. Denominator used was for male patients only (N=913 ZOLOFT; N=773 placebo).

*Major depressive disorder and other premarketing controlled trials.

**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 and pharyngitis.

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 20

Associated with Discontinuation in Placebo-Controlled Clinical Trials

Table 3 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*, OCD, panic disorder and PTSD.

**TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH
DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS**

Adverse Event	Major Depressive Disorder/Other*, OCD, Panic Disorder and PTSD combined (N=2198)	Major Depressive Disorder/Other* (N=861)	OCD (N=533)	Panic Disorder (N=430)	PTSD (N=374)
Agitation	1%	1%	–	2%	–
Diarrhea	2%	2%	2%	1%	–
Dizziness	1%	–	1%	–	–
Dry Mouth	–	1%	–	–	–
Dyspepsia	–	–	–	1%	–
Ejaculation Failure ⁽¹⁾	1%	1%	1%	2%	–
Headache	1%	2%	–	–	1%
Insomnia	2%	1%	3%	2%	–
Nausea	3%	4%	3%	3%	2%
Nervousness	–	–	–	2%	–
Somnolence	2%	1%	2%	2%	–
Tremor	–	2%	–	–	–

⁽¹⁾Primarily ejaculatory delay. Denominator used was for male patients only (N=271 major depressive disorder/other*; N=296 OCD; N=216 panic disorder; N=130 PTSD).

*Major depressive disorder and other premarketing controlled trials.

Male and Female Sexual Dysfunction with SSRIs

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

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

Table 4 below displays the incidence of sexual side effects reported by at least 2% of patients taking ZOLOFT in placebo-controlled trials.

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 21

TABLE 4

Treatment	Ejaculation failure (primarily delayed ejaculation)		Decreased libido	
	N (males only)	Incidence	N (males and females)	Incidence
ZOLOFT	913	14%	2198	6%
Placebo	773	1%	1877	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.

Other Adverse Events in Pediatric Patients—In approximately N=250 pediatric patients treated with ZOLOFT, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events, not appearing in Tables 1 and 2, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate in a controlled trial (N=187): hyperkinesia, twitching, fever, malaise, purpura, weight decrease, concentration impaired, manic reaction, emotional lability, thinking abnormal, and epistaxis.

Other Events Observed During the Premarketing Evaluation of ZOLOFT® (sertraline hydrochloride)—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.

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 22

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

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 23

hemorrhage, amenorrhea, leukorrhea; *Rare*: female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

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

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

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

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

Other Events Observed During the Postmarketing Evaluation of ZOLOFT—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), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, 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.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—ZOLOFT® (sertraline hydrochloride) is not a controlled substance.

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 24

Physical and Psychological Dependence—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

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

Among 634 overdoses in which sertraline hydrochloride was the only drug ingested, 8 resulted in fatal outcome, 75 completely recovered, and 27 patients experienced sequelae after overdose 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 overdose 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.

Overdose Management—Treatment should consist of those general measures employed in the management of overdose 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 overdose, 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[®]).

NDA_s 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 25

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosage for Adults

Major Depressive Disorder and Obsessive-Compulsive Disorder–ZOLOFT treatment should be administered at a dose of 50 mg once daily.

Panic Disorder and Posttraumatic Stress Disorder–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 or PTSD, 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 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 should be administered once daily, either in the morning or evening.

Dosage for Pediatric Population (Children and Adolescents)

Obsessive-Compulsive Disorder–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.

Dosage for Hepatically Impaired Patients

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

NDA 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 26

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder—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.

Posttraumatic Stress Disorder—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.

Obsessive-Compulsive Disorder and Panic Disorder—Although the efficacy of ZOLOFT beyond 10-12 weeks of dosing for OCD and Panic Disorder has not been systematically demonstrated in controlled trials, both are chronic conditions, and it is reasonable to consider continuation of a responding patient. Dosage adjustments 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.

Switching Patients to or from a Monoamine Oxidase Inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with ZOLOFT. In addition, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

ZOLOFT Oral 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 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.

NDA's 19-839/S-033 & 20-990/S-001
Approved Labeling Enclosure
Page 27

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 0049-4960-50 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 0049-4900-66 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 0049-4910-66 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 controlled room temperature, 59° to 86°F (15° to 30°C).

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 controlled room temperature, 59° to 86°F (15° to 30°C).

Rx only

©2001 Pfizer Inc



Distributed by

Roerig

Division of Pfizer Inc, NY, NY 10017

Printed in U.S.A.

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

/s/

Russell Katz
10/12/01 03:02:04 PM