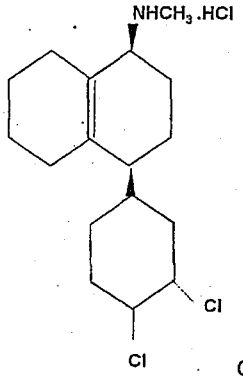
PRODUCT INFORMATION

ZOLOFT
(sertraline hydrochloride)

NAME OF THE DRUG

ZOLOFT (sertraline hydrochloride) is an antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name (1S,4S)-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:



CAS NO. 79559-97-0

DESCRIPTION

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 film coated tablets containing sertraline hydrochloride equivalent to 50, 100 or 200mg sertraline and the following inactive ingredients:

Cellulose - microcrystalline
Calcium hydrogen phosphate
Hydroxypropyl cellulose
Sodium starch glycollate
Magnesium stearate
White opadry
Clear opadry

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 noradrenaline and dopamine neuronal reuptake. In-vitro studies have shown that sertraline has no significant affinity to 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 noradrenaline receptors as has been observed with other clinically effective drugs used to treat depression, OCD and panic disorder. Sertraline does not inhibit monoamine oxidase.

Drugs known to influence serotonin receptors in animals and isolated cell preparations have been used to investigate possible 5HT receptor abnormalities in patients with OCD. No clear picture has emerged, but OCD symptoms were worsened by meta-chlorophenylpiperazine (mCPP), a mixed agonist at serotonin receptors in untreated OCD patients in comparison to healthy controls, but not after patients had been treated with the non-selective 5HT reuptake inhibitor clomipramine. Tricyclic antidepressants without SRI effects have no efficacy in OCD.

Clinical Trials

Major Depression

The efficacy of ZOLOFT in the treatment of a major depressive episode was established in controlled trials of six to eight weeks in outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder. Efficacy and safety have been established in studies up to 24 weeks.

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 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 hospitalised depressed patients has not been adequately studied. A study of depressed outpatients who had responded to ZOLOFT during an initial eight-week open treatment phase and were then randomised to continuation on ZOLOFT or placebo demonstrated a significantly lower relapse rate over the next eight weeks for patients taking ZOLOFT compared to those on placebo. 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.

Obsessive Compulsive Disorder (OCD)

The efficacy and safety of ZOLOFT in the treatment of OCD were established in three eight to twelve week controlled trials of non-depressed outpatients with mild, moderate, or severe OCD, diagnosed on the basis of DSM-III or DSM-III-R criteria. Efficacy and safety were maintained in a 40 week continuation of the 12 week fixed-dose, placebo-controlled study. In patients with OCD, the obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning in order to meet the DSM-III-R diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable. In three double blind, multicenter, parallel group, placebo controlled trials, both clinically relevant and statistically significant improvements in response rates (40%) were noted in sertraline treatment groups.

In a 12-week double-blind fixed-dose placebo-controlled study in OCD, 26% of patients receiving placebo were regarded as responders to therapy, whereas 40% of patients receiving sertraline were regarded as responders.

Panic Disorder

The efficacy and safety of Zoloft in the treatment of panic disorder has been evaluated in four double-blind, placebo-controlled clinical trials for up to 12 weeks: two flexible dose studies and two fixed dose studies. At the last week of treatment (week 10 or 12), both flexible dose studies and one of the fixed dose studies showed statistically significant differences from placebo in favour of ZOLOFT in terms of mean change from baseline in the total number of DSM-III-R defined panic attacks (last observation carried forward analysis). As the flexible dose studies were of identical protocol, data for these investigations can be pooled. The mean number of full panic attacks at baseline was 6.2/week (N=167) in the ZOLOFT group and 5.4/week in the placebo group (N=175). At week 10 (last observation carried forward analysis), the mean changes from baseline were 4.9/week and 2.5/week for the ZOLOFT and placebo groups, respectively. The proportion of patients having no panic attacks at the final evaluation was 69% in the ZOLOFT group and 57% in the placebo group. The mean daily dose administered at the last week of treatment was approximately 120mg (range: 25-200mg) in the flexible dose studies. All patients entered into clinical trials had a DSM-IIIR diagnosis of panic disorder with or without agoraphobia. It was found in the flexible dose studies that initiating treatment at 25mg/day for one week led to a lower incidence of early discontinuations.

The primary efficacy measure was the number of DSM-III-R defined panic attacks occurring each week. Secondary efficacy variables measured included the Sheehan Panic and Anticipatory Anxiety Scale (PAAS), Hamilton Anxiety (HAM-A) Scale and the Clinical Global Impressions (CGI) rating of severity of Illness and Improvement.

The statistically significant superiority of sertraline over placebo in the treatment of panic disorder was demonstrated by the reduction in the number of panic attacks per week at study endpoint. Analyses of the secondary efficacy variables confirmed that the reduction in panic attack frequency was associated with significant improvement in a broad range of disease symptoms. No clear dose-dependency has been demonstrated over the 50 to 200mg/day dose range investigated in the fixed dose studies. Efficacy beyond 12 weeks has not been assessed.

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.

The effects of food on the bioavailability of sertraline were studied in subjects administered a single dose with and without food. 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

decreased from 8 hours post-dosing to 5.5 hours. These changes were not considered clinically significant. Animal studies indicate that sertraline has a large apparent volume of distribution.

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 radiolabelled 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 faeces, including 12-14% unchanged sertraline. Desmethylsertraline exhibits time-related, dose dependent increases in AUC $_{(0\text{-}24\ hour)}$ 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 radiolabelled ^{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).

Age – Sertraline plasma clearance were compared in male and female young subjects (18-45 years) and elderly subjects ($\geq$ 65 years) in an open-label, multiple-dose study. Eleven subjects in each group received sertraline once daily for 30 days according to a titrated regimen up to 200 mg/day. No significant differences in C_{max}, AUC or elimination half-life were found for the young women or the elderly of either sex. In comparison, C_{max} and AUC were lower and half-life shorter in young men. Thus the elimination of sertraline appears to be slightly more rapid in young males. Although these differences are statistically significant, they are unlikely to be clinically significant. The ratios of sertraline clearance to desmethylsertraline clearance of the four groups were similar.

Liver Disease – Sertraline is extensively metabolised by the liver. A single dose pharmacokinetic study in patients with mild, stable cirrhosis demonstrated a prolonged elimination half-life and increased AUC in comparison to normal subjects. If ZOLOFT is administered to patients with hepatic impairment, a lower or less frequent dose should be considered (refer to DOSAGE AND ADMINISTRATION).

Renal Disease – In patients with mild to severe renal impairment (creatinine clearance 50– < 20 mL/min) single dose pharmacokinetic parameters ($AUC_{(0\text{-}inf)}$, C_{max}, T_{max}) are not significantly different compared with controls. However, steady state pharmacokinetics have not been adequately studied and caution is advised when treating these patients.

INDICATIONS

ZOLOFT (sertraline hydrochloride) is indicated for the treatment of major depression, obsessive compulsive disorder (OCD) and panic disorder

CONTRAINDICATIONS

ZOLOFT is contraindicated in patients with a known hypersensitivity to sertraline.

Monoamine Oxidase Inhibitors (MAOI)

Cases of serious reactions, sometimes fatal, have been reported in patients receiving ZOLOFT in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI, selegiline, and the reversible MAOI (reversible inhibitor of monoamine oxidase – RIMA), moclobemide. Some cases presented with features resembling the serotonin syndrome. Similar cases, sometimes fatal, including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma have been reported with other antidepressants during combined treatment with an MAOI and in patients who have recently discontinued an antidepressant or an antiobsessional drug and have been started on an MAOI. 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

Withdrawal Reactions – These have been reported with SSRI antidepressants, including ZOLOFT, when they have been abruptly discontinued or reduced. Dosage should be tapered when discontinuing treatment, particularly for those taking high doses.

Other Serotonergic Drugs - Coadministration of sertraline with other drugs which enhance serotonergic neurotransmission, such as tryptophan or fenfluramine, should be undertaken only with caution and avoided whenever possible due to the potential for pharmacodynamic interaction.

Switching from Other Antidepressants or Antiobsessional Drugs – There is limited controlled experience regarding the optimal timing of switching from other antidepressants to ZOLOFT. Care and prudent medical judgement should be exercised when switching, particularly from long-acting agents. The duration of washout which should intervene when switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established. Until further data are available, serotonergic drugs, eg fenfluramine, tryptophan, should not be used in conjunction with ZOLOFT.

Activation of Mania/Hypomania – During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder treated with other antidepressant and antiobsessional drugs.

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 0.5 to 1 kg weight loss, versus smaller changes on placebo. Only rarely (<0.1%) have sertraline patients been discontinued for weight loss.

Seizures – Seizures are a potential risk with drugs used to treat depression, OCD and panic disorder. ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. ZOLOFT should

therefore be avoided in patients with unstable epilepsy. Its use in patients with controlled epilepsy should be carefully monitored. The drug should be discontinued in any patient who develops seizures.

Suicide – The possibility of a suicide attempt is inherent in depression 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.

Weak Uricosuric Effect – ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with ZOLOFT.

Use in Patients with Concomitant Illness – Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or haemodynamic 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.

Use in Hepatic Insufficiency – ZOLOFT is extensively metabolized by the liver. A single dose pharmacokinetic study in patients with mild, stable cirrhosis demonstrated a prolonged elimination half-life and increased AUC in comparison to normal subjects. The use of ZOLOFT in patients with hepatic disease must be approached with caution. If ZOLOFT is administered to patients with hepatic impairment, a lower or less frequent dose should be considered. No information is available about long-term use of ZOLOFT in the presence of hepatic impairment.

Use in renal insufficiency - Since sertraline is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination.

In patients with mild to severe renal impairment (creatinine clearance 50-< 20mL/min) single dose pharmacokinetic parameters ($AUC_{(0\text{-}inf)}$, C_{max}, T_{max}) were not significantly different compared with controls.

However steady state pharmacokinetics of sertraline have not been adequately studied in this patient group and caution is advised when treating these patients with renal impairment.

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

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

- Patients should be told that, although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor or mental skills in laboratory experiments, drugs that act on the central nervous system may affect some individuals adversely.

- 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 in depressed patients is not advised.

- Patients should be asked about use of over-the-counter (OTC) drug products, and told that, while no adverse interaction of ZOLOFT with such 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.

Carcinogenicity, Mutagenicity

The carcinogenic potential of sertraline has not been fully elucidated. Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats (at doses up to 40 mg/kg), giving rise to plasma drug exposure levels similar to or slightly higher than that achieved following the maximum recommended human dose of 200 mg. There was a dose-related increase in the incidence of liver adenomas in male mice receiving sertraline at 10-40 mg/kg. 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; this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg 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.

Impairment of Fertility

A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (giving rise to plasma drug exposure levels similar to or slightly higher than that achieved following the maximum recommended human dose of 200 mg).

Use in Pregnancy.

CATEGORY B3

This category is defined as drugs which have been taken by only a limited number of pregnant women and women of child bearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects of the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Teratogenic Effects – Reproduction studies have been performed in rats and rabbits at doses up to 80 and 40 mg/kg, giving rise to plasma drug exposure levels similar to or slightly higher than that achieved following the maximum recommended human dose of 200 mg.

There was no evidence of teratogenicity at any dose level. However, sertraline was associated with delayed ossification in foetuses, probably secondary to effects on the dams.

Non-teratogenic Effects – There was also decreased neonatal survival following maternal administration of sertraline at doses giving rise to plasma drug exposure levels similar to or slightly higher than that achieved following the maximum recommended human dose of 200 mg. The decrease in pup survival was shown to be most probably due to in-utero exposure to sertraline. The clinical significance of these effects is unknown. Similar effects have been described with other antidepressants.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Zoloft should not be used during pregnancy unless in the judgement of the physician, the expected benefit justifies the risk to the foetus. If Zoloft is used in pregnancy, the physician should be aware that withdrawal reactions have been reported in some neonates whose mothers had been on SSRI antidepressants, including Zoloft, during pregnancy.

Women of childbearing potential should avoid becoming pregnant if taking Zoloft.

Labour and Delivery – The effect of ZOLOFT on labour and delivery in humans is unknown.

Use in lactation – Only limited data concerning sertraline levels in breast milk are available. However, in breast-fed infants whose mothers were taking sertraline, there have been reports of adverse effects. Because sertraline is excreted in human milk, breastfeeding while on Zoloft is not recommended.

Paediatric Use – Safety and effectiveness in children have not been established.

Geriatric Use – Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients.

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors - see CONTRAINDICATIONS.

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins - Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT to a patient taking another drug which is bound to protein may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound sertraline by other protein bound drugs.

Formal drug interaction studies have been performed with ZOLOFT. In a study comparing prothrombin time $AUC_{(0\text{-}120\ hr)}$ following dosing with warfarin (0.75 mg/kg) before and after 22 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.

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 the 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. There are, however, no controlled clinical trials with ZOLOFT in patients treated with lithium. Co-administration of sertraline with lithium may lead to a higher incidence of side effects. Caution is therefore advised if such concomitant administration is required. Accordingly, 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.

Drugs Metabolised by Cytochrome P450 (CYP) 2D6 – Many antidepressants, e.g. the SSRIs, including sertraline, and most tricyclic antidepressants, inhibit the biochemical activity of the drug metabolising isozyme cytochrome CYP 2D6 (debrisoquine hydroxylase) and thus may increase the plasma concentrations of co-administered drugs that are metabolised by CYP 2D6. The drugs for which this potential interaction is of greatest concern are those metabolised primarily by 2D6 and which have a narrow therapeutic index, e.g. the tricyclic antidepressants 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 CYP 2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the antidepressants 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 metabolised by CYP 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.

Hypoglycaemic 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. No interaction was observed with glibenclamide.

Cardiovascular – ZOLOFT (100 mg), when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol. No interaction was observed with digoxin.

Cimetidine – A controlled study in 13 healthy volunteers showed that co-administration of cimetidine caused a statistically significant increase in sertraline mean $AUC_{(0\text{-inf})}$ by 50%, C_{max} by 24% and $T_{1/2}$ by 26%. The apparent greater effect on sertraline AUC than on half-life is consistent with reductions in first pass metabolism and total body clearance. Significant increases in some desmethylsertraline parameters were also found. Cimetidine is likely to exert

inhibitory effects on various cytochrome P-450 enzymes which are responsible for the N-dealkylation pathway important in the metabolism of sertraline and many other drugs.

Side effects considered possibly related to treatment were reported for 4 of the 13 subjects after administration of sertraline with placebo. None of these led to discontinuation but two subjects were discontinued because of misdosing. There were no laboratory test abnormalities considered possibly related to treatment.

The clinical significance of the pharmacokinetic interaction between sertraline and cimetidine is uncertain. The magnitude of the effect is relatively small compared to the known intersubject variability. Moreover, there are no data to indicate that the magnitude of the antidepressant effect of sertraline is directly related to plasma concentration. Hence, there are no firm reasons to suggest an alteration in the sertraline dosage regimen in patients receiving cimetidine.

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.

Other Interactions

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

CNS Depressants and 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 in depressed patients is not recommended.

Driving, Use of Machinery – Clinical pharmacology studies have shown that ZOLOFT appears to have no effect on psychomotor performance. However, as drugs used to treat depression, OCD or panic disorder may impair the mental or physical attributes required for the performance of potentially hazardous tasks such as driving a car or using machinery the patient should be cautioned accordingly.

ADVERSE REACTIONS

Commonly Observed – The most commonly observed adverse events associated with the use of ZOLOFT and not seen at an equivalent incidence among placebo treated patients were: gastrointestinal complaints, including nausea, diarrhoea/loose stools, anorexia and dyspepsia; tremor; dizziness; insomnia; somnolence; increased sweating; dry mouth; and male sexual dysfunction (principally ejaculatory delay).

Associated with Discontinuation of Treatment – Fifteen percent of 2710 subjects who received ZOLOFT in premarketing multiple dose clinical trials discontinued treatment due to an adverse event. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhoea/loose stools, nausea and fatigue.

In the total safety database for panic disorder, 14% of patients discontinued treatment due to an adverse event. The most common events leading to discontinuation were nausea (2.6%), insomnia (2.3%) and agitation (2.1%).

In a 12-week double-blind placebo-controlled study in OCD, 73.4% of patients receiving placebo reported adverse experiences, whereas 93.8% of patients receiving sertraline reported adverse experiences.

Incidence in Controlled Clinical Trials – The table that follows enumerates adverse events that occurred at a frequency of 1% or more among ZOLOFT patients who participated in controlled trials comparing titrated ZOLOFT with placebo. Most patients received doses of 50 to 200 mg/day. The prescriber should be aware that these figures 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 which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

In the tabulations, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of approximately 2700 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 table and those reported in terms so general as to be uninformative. 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 (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); 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.

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials*

Adverse Experience	(Percent of Patients Reporting)	
	ZOLOFT (N=861)	Placebo (N=853)
Autonomic Nervous System Disorders		
Mouth Dry	16.3	9.3
Sweating Increased	8.4	2.9
Cardiovascular		
Palpitations	3.5	1.6
Chest Pain	1.0	1.6
Centr. & Periph. Nerv. System Disorders		
Headache	20.3	19.0
Dizziness	11.7	6.7
Tremor	10.7	2.7
Paresthesia	2.0	1.8
Hypoesthesia	1.7	0.6
Twitching	1.4	0.1
Hypertonia	1.3	0.4
Convulsions (inc myoclonus)†	1.1	0

Disorders of Skin and Appendages		
Rash	2.1	1.5
Urticaria†	1.1	0
Gastrointestinal Disorders		
Nausea	26.1	11.8
Diarrhoea/Loose Stools	17.7	9.3
Constipation	8.4	6.3
Dyspepsia	6.0	2.8
Vomiting	3.8	1.8
Flatulence	3.3	2.5
Anorexia	2.8	1.6
Abdominal Pain	2.4	2.2
Appetite Increased	1.3	0.9
General		
Fatigue	10.6	8.1
Pain†	2.7	0.9
Hot Flushes	2.2	0.5
Fever	1.6	0.6
Back Pain	1.5	0.9
Malaise†	1.1	0
Metabolic and Nutritional Disorders		
Weight increase†	3.5	0
Weight loss†	1.9	0.9
Thirst	1.4	0.9
Musculoskeletal System Disorders		
Arthralgia†	2.2	1.4
Myalgia	1.7	1.5
Psychiatric Disorders		
Insomnia	16.4	8.8
Sexual Dysfunction - Male[1]	15.5	2.2
Libido decreased†	15.5	2.5
Somnolence	13.4	5.9
Agitation	5.6	4.0
Nervousness	3.4	1.9
Depersonalisation†	2.7	1.9
Anxiety	2.6	1.3
Paroniria†	2.2	1.0
Amnesia†	1.9	1.4
Yawning	1.9	0.2
Sexual Dysfunction - Female[2]	1.7	0.2
Concentration Impaired	1.3	0.5
Thinking abnormal†	1.1	0
Teeth grinding†	1.1	0
Apathy†	1.1	0.9
Reproductive		
Menstrual Disorder[2]	1.0	0.5
Vaginal haemorrhage‡	2.1	0
Respiratory System Disorders		
Respiratory disorder†	4.3	4.7
Rhinitis	2.0	1.5
Pharyngitis	1.2	0.9
Coughing†	1.1	1.9

Dyspnoea†	1.1	0.9
Special Senses		
Vision Abnormal	4.2	2.1
Tinnitus	1.4	1.1
Taste Perversion	1.2	0.7
Earache†	1.1	0.9
Urinary System Disorders		
Polyuria†	1.8	1.0
Micturition Frequency	2.0	1.2
Micturition Disorder	1.4	0.5
Urinary retention†	1.5	0

* Events reported by at least 1% of patients treated with ZOLOFT are included.
† Based on OCD placebo controlled clinical trials (n=340 active treatment, n=209 placebo).
(1) - % based on male patients only: 271 ZOLOFT (primarily ejaculatory delay) and 271 placebo patients.
(2) - % based on female patients only: 590 ZOLOFT and 582 placebo patients.

In placebo-controlled clinical trials, 430 patients with panic disorder were treated with ZOLOFT in doses of 25-200mg/day. Adverse events which appeared to be dose-related include dry mouth, increased sweating and ejaculatory delay.

Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline hydrochloride): During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 2700 subjects. 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 indications other than depression. 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.

Autonomic Nervous System Disorders - *Infrequent*: flushing, mydriasis, increased saliva, cold clammy skin; *Rare*: pallor.

Cardiovascular - *Infrequent*: postural dizziness, hypertension, hypotension, postural hypotension, oedema, dependent oedema, periorbital oedema, peripheral oedema, peripheral ischaemia, syncope, tachycardia; *Rare*: precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins.

Central and Peripheral Nervous System Disorders - *Frequent*: confusion; *Infrequent*: ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo; *Rare*: local anaesthesia, coma, convulsions, dyskinesia, dysphoria, hyporeflexia, hypotonia, ptosis.

Disorders of Skin and Appendages - *Infrequent*: acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin; *Rare*: bullous eruption, dermatitis, erythema multiforme, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discolouration, abnormal skin odour, urticaria.

Endocrine Disorders - *Rare*: exophthalmos, gynaecomastia.

Gastrointestinal Disorders - *Infrequent*: dysphagia, eructation; *Rare*: diverticulitis, faecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, haemorrhoids, hiccup, melaena, haemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative stomatitis, tenesmus, tongue oedema, tongue ulceration.

General - *Frequent*: asthenia; *Infrequent*: malaise, generalized oedema, rigors, weight decrease, weight increase; *Rare*: enlarged abdomen, halitosis, otitis media, aphthous stomatitis.

Haematopoietic and Lymphatic - *Infrequent*: lymphadenopathy, purpura; *Rare*: anaemia, anterior chamber eye haemorrhage.

Metabolic and Nutritional Disorders - *Rare*: dehydration, hypercholesterolaemia, hypoglycaemia.

Musculoskeletal System Disorders - *Infrequent*: arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness; *Rare*: hernia.

Psychiatric Disorders - *Infrequent*: abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide ideation and attempt, teeth-grinding, abnormal thinking; *Rare*: hysteria, somnambulism, withdrawal syndrome.

Reproductive - *Infrequent*: dysmenorrhoea[2], intermenstrual bleeding[2]; *Rare*: amenorrhoea[2], balanoposthitis[1], breast enlargement[2], female breast pain[2], leukorrhoea[2], menorrhagia[2], atrophic vaginitis[2].

(1) - % based on male subjects only: 1005
(2) - % based on female subjects only: 1705

Respiratory System Disorders - *Infrequent*: bronchospasm, coughing, dyspnoea, epistaxis; *Rare*: bradypnea, hyperventilation, sinusitis, stridor.

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

Urinary System Disorders - *Infrequent*: dysuria, face oedema, nocturia, polyuria, urinary incontinence; *Rare:* oliguria, renal pain, urinary retention.

Laboratory Tests – In man, asymptomatic elevations in serum transaminases (AST and ALT) have been reported infrequently (approximately 0.8%) in association with ZOLOFT 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.

Rare cases of withdrawal reactions have been reported (see PRECAUTIONS).

Rare cases of hyponatraemia 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 reports were associated with older, particularly female, patients, and patients taking diuretics or other medications.

The side effect profile commonly observed in double-blind, placebo controlled studies in patients with OCD and panic disorder was similar to that observed in clinical trials in patients with depression.

Post-Marketing Data

In addition to treatment-related adverse events reported in the clinical trials, the following treatment emergent adverse events possibly, probably or certainly related to Zoloft have been reported at the frequencies below.

Common:	≥ 1%	and	< 10%
Infrequent:	≥ 0.1%	and	< 1%
Rare::	≥ 0.01%	and	< 0.1%

Cardiovascular - *Rare:* atrial arrhythmia, bradycardia

Central and Peripheral Nervous System Disorders - *Infrequent:* movement disorders (such as extrapyramidal symptoms and gait abnormalities)

Disorders of Skin and Appendages - *Rare:* angiooedema, Stevens-Johnson syndrome, toxic epidermal necrolysis

Endocrine Disorders - *Rare:* hyperprolactinaemia

Haematopoietic and Lymphatic - *Rare: leukopenia, thrombocytopenia*

Gastrointestinal Disorders - *Rare:* pancreatitis

Liver/Biliary - *Rare:* hepatic failure, hepatitis, jaundice

Psychiatric Disorders - *Common:* thinking abnormal; *Rare:* manic reaction, neuroleptic malignant syndrome, psychosis

Reproductive (Female) - *Rare:* galactorrhoea

Special Senses - *Infrequent:* eye pain, *Rare:* visual field defect

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence – ZOLOFT has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. However, the premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behaviour. As with any CNS active drug, 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 behaviour).DOSAGE AND ADMINISTRATION

Major Depression; Obsessive Compulsive Disorder

Initial Treatment – ZOLOFT (sertraline hydrochloride) treatment should be initiated with a dose of 50 mg once daily. The usual therapeutic dose for depression is 50mg/day. While a relationship between dose and antidepressant or antiobsessive effect has not been established, patients were dosed in a range of 50 - 200 mg/day in the clinical trials demonstrating the antidepressant or antiobsessive effectiveness of ZOLOFT. Consequently, patients not responding to a 50 mg/day 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. The onset of therapeutic effect may be seen within 7 days; however for full activity 2 to 4 weeks are usually necessary for depression and even longer for OCD.

If no effect is apparent after six to eight weeks, discontinuation of treatment should be considered. There are insufficient data regarding benefits from treatment beyond one year. Studies of efficacy did not examine the role of psychotherapy.

Panic Disorder

Initial treatment - Therapy for panic disorder should commence at 25mg/day, increasing to 50mg/day after one week. This dosage regimen has been demonstrated to reduce the frequency of early treatment-emergent side effects commonly experienced on initiation of treatment of panic disorder.

The daily dose for all indications may be increased in 50 mg increments over a period of weeks. Dose titrations in 50mg increments will depend on tolerability and clinical response. The interval between dose increments should be at least one week. The maximum recommended dose of sertraline is 200mg/day.

The onset of therapeutic effect may be seen after a week, however, most responders can be expected to show a good response within 2 to 4 weeks.

During prolonged maintenance therapy for any indication, dosage should be kept at the lowest effective level. The long term efficacy of ZOLOFT in panic disorder has not been established.

ZOLOFT should be administered once daily, either in the morning or evening. ZOLOFT may be administered with or without food.

As indicated under PRECAUTIONS, particular care should be used in patients with hepatic and/or renal impairment.

Use in the elderly requires no special precautions. The usual adult dosage is recommended.

Maintenance/Continuation/Extended Treatment – There is evidence to suggest that depressed patients responding during an initial 8 week treatment phase will continue to benefit during an additional 16 weeks of treatment. While there are insufficient data regarding benefits from treatment beyond 24 weeks, it is generally agreed among expert psychopharmacologists that acute episodes of depression require several months or longer of sustained pharmacological therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.
Discontinuation should be accomplished by a gradual reduction in dosage.

OVERDOSAGE

On the evidence available, ZOLOFT has a wide margin of safety in overdose. Overdoses of ZOLOFT alone up to 6g have been reported. Deaths involving ZOLOFT in combination with other drugs and/or alcohol have been reported. Therefore any overdosage should be treated aggressively.

Management of Overdoses – Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose.

Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

There are no specific antidotes for ZOLOFT.

Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit.

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

PRESENTATION

ZOLOFT capsule-shaped tablets, containing sertraline hydrochloride equivalent to 50, 100 or 200mg of sertraline, are packaged in blister packs of 28 tablets.

ZOLOFT 50 mg tablets: white film coated tablets marked with the Pfizer logo on one side and "ZLT" scoreline "50" on the other.

ZOLOFT 100 mg tablets: white film coated tablets marked with the Pfizer logo on the one side and "ZLT-100" on the other.

ZOLOFT 200 mg tablets: white film coated tablets marked with the Pfizer logo on the one side and "ZLT-200" on the other.

NAME AND ADDRESS OF SPONSOR

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