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 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 or 100 mg 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.

NAME AND ADDRESS OF SPONSOR

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