AUSTRALIAN PRODUCT INFORMATION

ZOLOFT®

(sertraline hydrochloride) tablet

1 NAME OF THE MEDICINE

Sertraline hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOLOFT 50 mg tablets contain 50 mg sertraline (as hydrochloride) as the active ingredient.

ZOLOFT 100 mg tablets contain 100 mg sertraline (as hydrochloride) as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ZOLOFT 50 mg: White, film-coated, capsular shaped tablets debossed with "VLE" on one side and with the code "ZLT" including "50" on the other side. The tablet has a functional score line between "ZLT" and "50".

ZOLOFT 100mg: White, film-coated, capsular shaped tablets debossed with "VLE" on one side and with the code "ZLT" including "100" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Children and Adolescents

ZOLOFT (sertraline hydrochloride) is indicated for the treatment of children (aged 6 years of age and older) and adolescents with OCD.

Adults

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

ZOLOFT (sertraline hydrochloride) is indicated for the treatment of social phobia (social anxiety disorder) and the prevention of its relapse.

ZOLOFT (sertraline hydrochloride) is indicated for the treatment of premenstrual dysphoric disorder (PMDD) as defined by DSM-IV criteria.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Children and adolescents (6-18 years)

Obsessive Compulsive Disorder

The administration of ZOLOFT in children with OCD (ages 6-12 years) is recommended to commence at 25 mg/day (half a 50 mg tablet) for the first week and then increasing to 50 mg/day. Adolescents (ages 13-18 years) may commence at 50 mg/day. Clinical effects may be noted after 2 weeks of treatment but clinical responses should be monitored for 6 weeks before any increase in dose. In children, a dose of 200 mg/day should not be exceeded. Sertraline has an elimination half-life of approximately 26 hours; a once daily dose in the morning is recommended.

Adults (18 years and older)

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 and OCD is 50 mg/day. While a relationship between dose and antidepressant and anti-obsessive effect has not been established, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the antidepressive and anti-obsessive 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 possibly even longer for OCD.

Following initial response, sertraline has been associated with sustained efficacy, safety and tolerability in up to 2 years of treatment of OCD. If no effect is apparent after six to eight weeks, discontinuation of treatment should be considered. Studies of efficacy did not examine the role of psychotherapy.

Panic Disorder

Initial Treatment – Therapy for panic disorder should commence at 25 mg/day (half a 50 mg tablet), increasing to 50 mg/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 long-term efficacy of ZOLOFT in panic disorder has not been established.

Social Phobia (Social Anxiety Disorder)

Initial treatment – Therapy for social phobia (social anxiety disorder) should commence at 25 mg/day (half a 50 mg tablet), increasing to 50 mg/day after one week.

Premenstrual Dysphoric Disorder

ZOLOFT treatment should be initiated with a dose of 50 mg/day either continuously (every day of the menstrual cycle) or intermittently (by starting 14 days prior to the anticipated onset of menstruation through to the first full day of menses and repeating with each cycle), depending on physician assessment.

Patients not responding to a 50 mg/day dose may benefit from dose increases (at 50 mg increments/menstrual cycle) up to 150 mg/day when dosing daily throughout the menstrual cycle, or 100 mg/day when dosing during the luteal phase of the menstrual cycle. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilised at the beginning of each luteal phase dosing period.

Dosage adjustments, which may include changes between dosage regimens (e.g., daily throughout the menstrual cycle versus during the luteal phase of the menstrual cycle), may be needed to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

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.

General

The daily dose for all indications may be increased in 50 mg increments over a period of weeks. However, dose titrations in 50 mg 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 200 mg/day.

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

During prolonged maintenance therapy for any indication, dosage should be kept at the lowest effective level.

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

As indicated under Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, particular care should be taken in patients with hepatic impairment.

Method of Administration

Oral administration.

4.3 CONTRAINDICATIONS

ZOLOFT is contraindicated in patients with known hypersensitivity to sertraline.

Concomitant use in patients taking pimozide is contraindicated (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Monoamine Oxidase Inhibitors

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, the reversible MAOI (reversible inhibitor of monoamine oxidase – RIMA), moclobemide, and MAOI drugs, e.g., linezolid (an antibiotic that is a reversible non-selective MAOI) and methylene blue. 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 a MAOI and in patients who have recently discontinued an antidepressant or an anti-obsessional drug and have been started on a MAOI. ZOLOFT should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting a MAOI.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serotonin Syndrome or Neuroleptic Malignant Syndrome

The development of potentially life-threatening syndromes like serotonin syndrome (SS) or neuroleptic malignant syndrome (NMS) has been reported with selective serotonin reuptake inhibitors (SSRIs), including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of serotonergic drugs (including amphetamines, triptans and opioids (e.g., fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone, pentazocine), with drugs that impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. SS symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Some signs of SS, including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes resemble NMS. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome (see Section 4.3 CONTRAINDICATIONS).

Other Serotonergic Drugs

Coadministration of SSRIs such as sertraline with other drugs that enhance the effects of serotonergic neurotransmission, such as amphetamines, tryptophan, phentermine, fentanyl and its analogues, tramadol, 5-HT agonists, dextromethorphan, tapentadol, pethidine or methadone should be undertaken only with caution and avoided whenever possible due to the potential for pharmacodynamic interaction.

St John's Wort

Concomitant use of the herbal remedy St John's wort (*Hypericum perforatum*) in patients receiving SSRIs should be avoided since there is a possibility of serotonergic potentiation.

Switching from Other Antidepressants or Anti-obsessional Drugs

There is limited controlled experience regarding the optimal timing of switching from other antidepressants or anti-obsessional drugs to ZOLOFT. Care and prudent medical judgement should be exercised when switching, particularly from long-acting agents. The duration of a washout period for switching from one SSRI to another has not been established.

QTc Prolongation/Torsade de Pointes (TdP)

Cases of QTc prolongation and TdP have been reported during post-marketing use of sertraline. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP. Therefore, sertraline should be used with caution in patients with risk factors for QTc prolongation (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Activation of Mania/Hypomania

During pre-marketing 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 anti-obsessional drugs.

Hyperkinesia has been noted in paediatric patients treated with sertraline for OCD, with an incidence of 8/53 (15.1%) for sertraline versus 3/54 (5.6%) for placebo in 6 to 12-year-olds, and 0/39 (0%) for sertraline versus 1/41 (2.4%) for placebo in 13- to 17-year-olds.

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. In paediatric patients, weight loss was seen in 2/53 (3.8%) versus 0/54 (0%) of 6- to 12-year-old patients and 3/39 (7.7%) versus 0/41 (0%) of 13- to 17-year-olds treated with sertraline versus placebo. It is recommended that paediatric patients receiving long-term treatment should be monitored for weight and growth, consistent with good medical care.

Seizures

Seizures are a potential risk with antidepressant and anti-obsessional drugs. Seizures were reported in three out of 4000 patients (0.08%) treated with ZOLOFT in the development programme for depression. No seizures were reported in patients treated with sertraline in the development programme for panic. During the development programme for OCD, four out of 1801 patients (0.2%) exposed to ZOLOFT experienced seizures. In the paediatric OCD trial programme, the incidence of seizures in the adolescent (13 to 17 years old) population was 3/163 (1.8%) on sertraline compared with 0/41 (0%) on placebo. Seizures/convulsions were not noted in 6- to 12-year-old patients. In all these cases, the relationship with sertraline therapy was uncertain. Since ZOLOFT has not been evaluated in patients with a seizure disorder it should be avoided in patients with unstable epilepsy; patients with controlled epilepsy should be carefully monitored. ZOLOFT should be discontinued in any patient who develops seizures.

Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk of suicide must be considered in all depressed patients.

Because of the coexistence of depression in patients with other psychiatric disorders, such as OCD, panic disorder, social phobia (social anxiety disorder) and PMDD, the same precautions should be observed when treating patients with these disorders as when treating patients with depression.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the initial treatment period (generally the first one to two months) in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients treated with placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

A further pooled analysis of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed the increased risk of suicidal thinking and behaviour (suicidality) during the initial treatment period (generally the first one to two months) extends to young adults (aged 18 to 24 years) with major depressive disorder (MDD) and other psychiatric disorders. These studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric), should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

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.

Sexual Dysfunction

SSRIs may cause symptoms of sexual dysfunction (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

Abnormal Bleeding/Haemorrhage

Bleeding abnormalities have been reported with the use of SSRIs (including purpura, haematoma, epistaxis, vaginal bleeding, ecchymoses, gastrointestinal bleeding and life-threatening haemorrhage). This risk may be potentiated by concurrent use of atypical antipsychotics and phenothiazines, most tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin or other medicines that affect coagulation. ZOLOFT should therefore be used with caution in patients concomitantly treated with medicines that increase the risk of bleeding or in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

Postpartum haemorrhage

SSRI/SNRIs may increase the risk of postpartum haemorrhage (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Hyponatraemia

Hyponatraemia may occur as a result of treatment with SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs) including sertraline. In many cases, hyponatraemia appears to be the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium levels lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatraemia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in the Elderly). Discontinuation of sertraline should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatraemia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness that may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest and death.

Bone Fractures

Epidemiological studies show an increased risk of bone fractures in patients receiving serotonin reuptake inhibitors (SRIs) including sertraline. The mechanism leading to this risk is not fully understood.

Diabetes/Loss of Glycaemic Control

Cases of new-onset diabetes mellitus have been reported in patients receiving SSRIs including ZOLOFT. Loss of glycaemic control including both hyperglycaemia and hypoglycaemia has also been reported in patients with and without pre-existing diabetes. Patients should therefore be monitored for signs and symptoms of glucose fluctuations. Diabetic patients especially should have their glycaemic control carefully monitored since their dosage of insulin and/or concomitant oral hypoglycaemic drug may need to be adjusted.

Angle-Closure Glaucoma

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

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 (ECG) 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.

Symptoms Associated with Discontinuation

During marketing of ZOLOFT and other SSRIs and SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors) there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paraesthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with ZOLOFT. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), 4.6 FERTILITY, PREGNANCY AND LACTATION, and 4.2 DOSE AND METHOD OF ADMINISTRATION).

Drug Abuse and Dependence

In human studies, sertraline has not demonstrated potential for abuse. In a placebo-controlled, double-blind, randomised study of comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential, such as euphoria or drug liking. 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 behaviour).

Electroconvulsive Therapy

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

Use in Hepatic Impairment

Sertraline is extensively metabolised by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis administered sertraline 50 mg/day for 21 days demonstrated a prolonged elimination half-life and approximately a three-fold greater AUC and C_{max} for sertraline and a two-fold greater AUC and C_{max} for the metabolite in comparison to normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of sertraline in patients with hepatic disease should be approached with caution. Patients with moderate and severe hepatic impairment have not been studied. A lower or less frequent dose should be used in patients with hepatic impairment.

Use in Renal Impairment

Sertraline is extensively metabolised. Excretion of unchanged drug in urine is a minor route of elimination. In a study of patients with mild to moderate renal impairment (creatinine clearance 30 mL/min to 60 mL/min) or moderate to severe renal impairment (creatinine clearance 10 mL/min to 29 mL/min) administered sertraline 50 mg/day for 21 days multiple dose pharmacokinetic parameters (AUC_{0-24} or C_{max}) were not statistically significantly different compared to controls. Half-lives were similar and there were no differences in plasma protein binding of all the groups studied. This study indicates that, as expected from the low renal excretion of sertraline, ZOLOFT dosing does not have to be adjusted based on degree of renal impairment.

Use in the Elderly

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.

Paediatric Use

A total of 225 paediatric patients have completed OCD trials with sertraline. The safety profile of ZOLOFT in these paediatric studies is comparable to that observed in the adult OCD studies.

Long-term safety on cognitive, emotional, physical, and pubertal maturation in children and adolescents aged 6 to 16 years was evaluated in a long-term observational study for up to 3 years (see Section 5.1 PHARMACODYNAMIC PROPERTIES). Physicians must monitor paediatric patients on long-term treatment for abnormalities in growth and development.

Safety and effectiveness in paediatric patients below the age of 6 years have not been established.

Sertraline should not be used in children and adolescents below the age of 18 years for the treatment of major depressive disorder. The efficacy and safety of sertraline has not been satisfactorily established for the treatment of major depressive disorder in this age group.

Effects on Laboratory Tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Monoamine Oxidase Inhibitors

See Section 4.3 CONTRAINDICATIONS.

Pimozide

Increased pimozide levels have been demonstrated in a study of single low-dose pimozide (2 mg) with sertraline coadministration. Coadministration of pimozide and sertraline increased pimozide C_{max} and AUC by 35% and 37%, respectively. These increased levels did not significantly increase the QTc interval. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated. There are no data with pimozide at doses greater than 2 mg (see Section 4.3 CONTRAINDICATIONS).

Drugs that Prolong the QTc Interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g., TdP) is increased with concomitant use of other drugs that prolong the QTc interval (e.g., some antipsychotics and antibiotics) (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, QTc Prolongation/Torsade de Pointes and 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

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.

Coadministration of Drugs with Serotonergic Action

Sumatriptan

There have been rare post-marketing reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. If concomitant treatment with sertraline and sumatriptan is clinically warranted, appropriate observation of the patient is advised (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Other Serotonergic Drugs

See Sections 4.3 CONTRAINDICATIONS, Monoamine Oxidase Inhibitors and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Serotonin Syndrome or Neuroleptic Malignant Syndrome and Other Serotonergic Drugs.

St John's Wort

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Medicines that Interfere with Haemostasis (NSAIDs, Aspirin, Warfarin, etc)

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates the risk. Thus, patients should be cautioned about using such medicines concurrently with ZOLOFT.

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. However, in three formal interaction studies with diazepam, tolbutamide and warfarin respectively, sertraline was not shown to have any significant effects on the protein binding of the substrate (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Warfarin).

Warfarin

Coadministration of sertraline 200 mg daily with warfarin resulted in an 8% delay in normalisation of prothrombin time compared to placebo ($p < 0.02$). The clinical significance of this is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.

Lithium

In placebo-controlled trials in normal volunteers, the coadministration of sertraline with lithium did not significantly alter the lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. Coadministering sertraline with medications, such as lithium, which may act via serotonergic mechanisms, should be undertaken with caution in patients and appropriately monitored.

Phenytoin

A placebo-controlled trial in healthy volunteers given sertraline 200 mg and phenytoin 100 mg for 10 days did not produce statistically significant differences in phenytoin pharmacokinetic parameters between the sertraline and placebo groups. Nonetheless, it is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose. In addition, coadministration of phenytoin may cause a reduction of sertraline plasma levels.

Drugs Metabolised by Cytochrome P450 2D6

There is variability among antidepressants in the extent to which they inhibit the activity of isozyme cytochrome P450 (CYP) 2D6, 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. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the coadministered drug. 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 coadministered drug may be required. CYP 2D6 substrates with a narrow therapeutic index include tricyclic antidepressants (TCAs), class 1C antiarrhythmics such as propafenone and flecainide, and methadone. In formal interaction studies, sertraline 50 mg daily produced increases ($p < 0.001$) in desipramine C_{max} (44%) and AUC (mean 23% to 37%).

Drugs Metabolised by Other CYP Enzymes (CYP 3A3/4, CYP 2C9, CYP 2C19, CYP 1A2)

CYP 3A3/4

In vivo interaction studies have demonstrated that administration of sertraline for 17-21 days at the high dose of 200 mg daily did not statistically significantly inhibit the CYP 3A3/4 metabolism of carbamazepine or terfenadine. In addition, the administration of sertraline 50 mg daily for 14 days did not statistically significantly inhibit the CYP 3A3/4-mediated metabolism of alprazolam. The results of these studies suggest that sertraline is not likely to be a clinically important inhibitor of CYP 3A3/4.

Coadministration of sertraline with metamizole, which is an inducer of metabolising enzymes including CYP 2B6 and CYP 3A4 may cause a reduction in plasma concentrations of sertraline with potential decrease in clinical efficacy, therefore, caution is advised when metamizole and sertraline are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

CYP 2C9

The apparent lack of clinically significant effects of the chronic administration of sertraline at the high dose of 200 mg daily on plasma concentrations of tolbutamide, phenytoin and warfarin suggests that sertraline is not a clinically important inhibitor of CYP 2C9 (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Phenytoin and Warfarin).

CYP 2C19

The apparent lack of clinically significant effects of the chronic administration of sertraline at the high dose of 200 mg daily on plasma concentrations of diazepam suggests that sertraline is not a clinically important inhibitor of CYP 2C19 (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Other Drug Interactions).

CYP 1A2

An *in vitro* study indicates that sertraline is a weak inhibitor of CYP 1A2.

Other Drug Interactions

Formal drug interaction studies have been performed with sertraline. Changes in drug levels as a result of interactions have been demonstrated. The precise clinical significance of these changes is unknown.

Cimetidine

Coadministration of cimetidine caused a statistically significant increase in sertraline mean AUC by 50% and C_{max} by 24% and $T_{1/2}$ by 26%.

Atenolol/Digoxin

Sertraline had no effect on the beta-adrenergic blocking activity of atenolol. No interaction was observed with digoxin.

Diazepam

Coadministration of diazepam showed a statistically significant decrease in diazepam clearance of 32% from baseline compared to a 19% decrease with placebo. Tmax for desmethyldiazepam was also statistically significantly prolonged by 23% in the sertraline group versus a decrease in the placebo group.

Glibenclamide

No interaction was observed with glibenclamide.

Clozapine

As in the coadministration with other SSRIs, isolated cases of increased clozapine levels have been reported.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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

Pregnancy Category C

This category is defined as drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Neonates exposed to ZOLOFT, other SSRIs, or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.

Teratogenic Effects

Reproduction studies have been performed in rats and rabbits at doses up to 80 and 40 mg/kg, respectively, 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 fetuses, probably secondary to effects on the dams.

Non-teratogenic Effects

Observational studies have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to SSRIs, including sertraline, especially within the month prior to birth.

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 fetus. The use of SSRIs in the third trimester may result in a withdrawal state in the newborn infant.

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

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to

infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997 to 2005 found a PPHN risk ratio of 2.4 (95% CI, 1.2 to 4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI, 1.2 to 8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy".

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. If ZOLOFT is used during lactation, the physician should be aware that withdrawal reactions have been reported in some neonates whose mothers had been on SSRI antidepressants, including ZOLOFT.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. However, as psychotropic drugs 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events are listed within body system and categorised by frequency according to the following definitions:

Very common: ≥ 10%

Common: ≥ 1% and < 10%

Uncommon: ≥ 0.1% and < 1%

Rare: ≥ 0.01% and < 0.1%

Unknown: Cannot be estimated from available data

Placebo-Controlled Clinical Trial Data

The following adverse events occurred at a frequency of 1% or more among ZOLOFT patients and at least twice the frequency seen in placebo patients, who participated in placebo-controlled clinical trials (adults - depression, OCD, children and adolescents - paediatric OCD). In these clinical trials most patients received doses of 50 to 200 mg/day. These events are not necessarily related to ZOLOFT treatment.

Metabolism and nutrition disorders:

Common: Decreased appetite

Psychiatric disorders:

Very common: Insomnia

Common: Agitation, anxiety, bruxism, libido decreased, nervousness, nightmare, thinking abnormal

Nervous system disorders:

Very common: Tremor, somnolence, dizziness

Common: Convulsion (including myoclonus), hypoaesthesia, hyperkinesia, hypertonia, disturbance in attention

Eye disorders:

Common: Visual impairment

Cardiac disorders:

Common: Palpitations

Vascular disorders:

Common: Hot flush

Respiratory, thoracic and mediastinal disorders:

Common: Yawning

Gastrointestinal disorders:

Very common: Diarrhoea, nausea

Common: Vomiting, dry mouth, dyspepsia

Skin and subcutaneous tissue disorders:

Common: Rash, hyperhidrosis, urticaria

Renal and urinary disorders:

Common: Urinary retention

Reproductive system and breast disorders:

Common: Ejaculation disorder, sexual dysfunction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), vaginal haemorrhage, menstruation irregular

General disorders and administration site conditions:

Very common: Fatigue

Common: Malaise, pyrexia

Investigations:

Common: Weight increased, weight decreased

Other adverse events reported (incidence > 10%) and not meeting the above criteria were dry mouth, dizziness, diarrhoea/loose stools, headache and abdominal pain (paediatric OCD patients only).

In a 12-week placebo-controlled study in paediatric patients with OCD, adverse events of at least 5% incidence that were seen with a statistically significantly increased level for sertraline compared with placebo were headache, insomnia and agitation in 6-12 year olds. For 13-17 year olds, the comparable categories were insomnia, decreased appetite and tremor. Most of the effects seen were mild to moderate in severity. In these clinical trials, sexual dysfunction was not specifically reported. However, in common with all other SSRIs, sexual dysfunction in males and, to a lesser extent, females have been reported in adult studies.

The side effect profile commonly observed in double-blind, placebo controlled studies in patients with panic disorder, social phobia (social anxiety disorder) and PMDD was similar to that observed in clinical trials patients with depression.

Adverse Effects from Clinical Trials in Paediatric MDD

In clinical trials in children and adolescents aged 6 to 17 years with major depressive disorder the following adverse events were reported at a frequency of at least 2% of subjects and occurred at a rate of at least twice that of placebo: diarrhoea (9.5% vs 1.6%), agitation (6.3% vs 1.1%), decreased appetite (5.3% vs 1.1%), vomiting (4.2% vs 1.1%) hyperkinesia (2.6% vs 0.5%), dry mouth (2.1% vs 0.5%), tremor (2.1% vs 0%) and urinary incontinence (2.1% vs 0%). The incidence of discontinuation due to adverse events was 9% (n=17) with sertraline and 2.1 (n=4) with placebo. The most common reasons for discontinuation due to adverse events, whether or not related to sertraline, were aggression (1.6%), agitation (1.6%), suicidal ideation (1.6%), hyperkinesia (1.1%), suicide attempt (1.1%) and aggravated depression (1.1%).

In the safety analysis, suicide attempt was reported in the same number of patients in sertraline (2/189, 1.1%) and placebo (2/184, 1.1%) with an incidence of suicide attempts in sertraline-treated subjects of 1.1% (2 attempts in 2/189 subjects) versus 1.6% in placebo-treated subjects (3 attempts in 2/184 subjects). Suicidal ideation was reported by 3 sertraline-treated patients (1.6%) and no placebo treated patients. This difference is not statistically significant. Note that sertraline should not be used in children and adolescents to treat MDD (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Post-marketing Experience

In addition to the adverse events reported from the clinical trials above, the following adverse events, which are not necessarily related to ZOLOFT, as adverse events are also reported in the context of post-marketing exposure, when the relationship of these adverse events to ZOLOFT may not be differentiated clearly from effects of concomitant medications or disease states for which ZOLOFT was prescribed.

Blood and lymphatic system disorders:

Rare: Thrombocytopenia, leukopenia

Immune system disorders:

Uncommon: Hypersensitivity

Rare: Anaphylactoid reaction

Endocrine disorders:

Rare: Inappropriate antidiuretic hormone secretion, hyperprolactinaemia, hypothyroidism

Metabolism and nutrition disorders:

Common: Increased appetite

Rare: Diabetes mellitus, hyponatraemia, hypoglycaemia, hyperglycaemia

Psychiatric disorders:

Uncommon: Hallucination, aggression, confusional state, depressive symptoms, euphoric mood

Rare: Psychotic disorder, mania

Nervous system disorders:

Very common: Headache

Common: Hypertonia, paraesthesia

Uncommon: Syncope, muscle contractions involuntary, migraine

Rare: Coma, neuroleptic malignant syndrome, visual field defect

Unknown: amnesia. Also reported were signs and symptoms associated with serotonin syndrome, in some cases associated with concomitant use of serotonergic drugs, that included agitation, confusional state, hyperhidrosis, diarrhoea, pyrexia, hypertension, muscle rigidity and tachycardia

Eye disorders:

Uncommon: Mydriasis, periorbital oedema, eye pain

Ear and labyrinth disorders:

Common: Tinnitus

Cardiac disorders:

Uncommon: Tachycardia

Rare: Atrial arrhythmia, bradycardia, atrioventricular block, QTc prolongation and torsade de pointes, electrocardiogram QT prolonged, blood cholesterol increased

Vascular disorders:

Common: Hypertension

Uncommon: Haemorrhage, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal haemorrhage and gastrointestinal haemorrhage

Rare: Cerebrovascular vasoconstriction (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome), vasculitis

Respiratory, thoracic and mediastinal disorders:

Uncommon: Bronchospasm

Rare: Eosinophilic pneumonia

Unknown: Dyspnoea

Gastrointestinal disorders:

Common: constipation, abdominal pain

Uncommon: Gastrointestinal haemorrhage

Rare: Pancreatitis

Unknown: microscopic colitis

Hepatobiliary disorders:

Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased

Rare: Serious liver injury (including hepatitis, jaundice and hepatic failure)

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, alopecia

Rare: Serious exfoliative skin disorders (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis), angioedema, photosensitivity skin reaction

Musculoskeletal and connective tissue disorders:

Common: Arthralgia

Uncommon: Muscle spasms

Rare: Rhabdomyolysis, trismus

Unknown: Multiple acyl-coenzyme A dehydrogenase deficiency (MADD)-like disorder

Renal and urinary disorders:

Uncommon: haematuria, urinary incontinence

Rare: Enuresis

Reproductive system and breast disorders:

Rare: Priapism, galactorrhoea, gynaecomastia

Unknown: postpartum haemorrhage*

*This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.6 FERTILITY, PREGNANCY AND LACTATION).

General disorders and administration site conditions:

Common: Movement disorders (including extrapyramidal symptoms such as akathisia, dystonia and gait disturbance), chest pain, asthenia

Uncommon: Gait disturbance, oedema peripheral

Rare: Face oedema, drug withdrawal syndrome (symptoms following the discontinuation of sertraline have been reported and included agitation, anxiety, dizziness, headache, nausea and paraesthesia)

Investigations:

Rare: Platelet function test abnormal, increased coagulation times, laboratory test abnormal

Injury, poisoning and procedural complications:

Rare: Fracture

Discontinuation Symptoms:

Rare: Symptoms following the discontinuation of sertraline have been reported and included agitation, anxiety, dizziness, headache, nausea and paraesthesia

Post-marketing Safety Study SPRITES

An observational post-approval study of 941 patients aged 6 to 16 years was conducted to evaluate the long-term safety of treatment with sertraline (with and without psychotherapy) compared with psychotherapy on cognitive, emotional, physical, and pubertal maturation for up to 3 years. This study was conducted in clinical practice settings in children and adolescents with primary diagnoses of obsessive compulsive disorder, depression, or other anxiety disorders and evaluated cognition [assessed by the Trails B test and the Metacognition Index from the Behaviour Rating Inventory of Executive Function (BRIEF), behavioural/emotional regulation (assessed by the Behavioural Regulation Index from the BRIEF) and physical/pubertal maturation (assessed by standardised height/weight/body mass index (BMI) and Tanner Stage)]. Sertraline is approved in the paediatric population only for patients aged 6 years of age and older with OCD (see Section 4.1 THERAPEUTIC INDICATIONS).

Standardisation of each primary outcome measure based on sex and age norms showed that the overall results were consistent with normal development. No statistically significant differences were observed for the primary outcome measures, with the exception of weight. A statistically significant finding for standardised weight was observed in comparative analyses and observed mainly at higher doses of sertraline. However, the magnitude of the change in weight was small [mean (SD) change in standardised z-scores = 0.17 (0.6)].

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

On the evidence available, sertraline has a wide margin of safety in overdose. Overdoses in adults of 700 to 2100 mg have not resulted in serious symptoms. Ingestion of 4000 mg resulted in seizures in an adolescent. The largest known ingestion is 13.5 g with recovery reported. Another overdose of 2.5 g of sertraline alone resulted in death. Overdosage of 400 and 500 mg in two children have resulted in serotonin syndrome.

Signs and Symptoms

Symptoms of overdose include serotonin-mediated side effects such as electrocardiogram QT prolonged, TdP (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials), somnolence, gastrointestinal disturbances (such as nausea, diarrhoea and vomiting), tachycardia, tremor, agitation and dizziness. Other important adverse events reported with sertraline overdose (single or multiple drugs) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, stupor and syncope. Hyperthermia, increased respirations and cutaneous vasodilation have also been reported. Minor ECG abnormalities, palpitations, prolonged tachycardia and increased pulse rate have also been reported following paediatric overdose. Seizures have been reported rarely. Serotonin syndrome may result following significant overdose, and onset may be delayed. A death due to asthma exacerbation has been reported following sertraline overdose.

Deaths have been reported involving overdoses of sertraline, primarily in combination with other drugs and/or alcohol. Therefore any overdosage should be treated aggressively.

Elevated liver enzymes and elevated creatine phosphokinase levels have been noted following acute overdose. Hyponatraemia secondary to SIADH has been reported following overdose and has been severe enough to cause seizures.

Treatment of Overdosage

In managing overdosage, consider the possibility of multiple drug involvement. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. Establish and maintain an airway, ensure adequate oxygenation and ventilation, if necessary. Patients should be monitored for potential cardiovascular, gastrointestinal, or hepatic abnormalities. Also monitor for signs/symptoms of serotonin syndrome (mental status changes, hyperthermia, myoclonus, autonomic instability, high CK levels) and possible seizures.

There are no specific antidotes for sertraline. Activated charcoal should be considered in treating overdose and is most effective when administered within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Routine use of a cathartic with activated charcoal is not recommended as there is no evidence that cathartics reduce drug absorption and cathartics are known to cause adverse effects such as nausea, vomiting, abdominal cramps, electrolyte imbalances and occasionally hypotension.

Induction of emesis is not recommended because of the potential for CNS depression and seizures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

ZOLOFT is an antidepressant, the active ingredient sertraline hydrochloride is chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents.

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 (alpha1, alpha2, beta), cholinergic, gamma-aminobutyric acid (GABA), dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$) or benzodiazepine receptors; antagonism of such receptors has been hypothesised 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 antidepressant and anti-obsessional drugs. 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 obsessive-compulsive disorder (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

Adults

The efficacy of ZOLOFT in the treatment of a major depressive episode in adults 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 re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder (OCD)

Children and Adolescents

The effectiveness of ZOLOFT for the treatment of OCD was first demonstrated in a 12-week, multicentre, parallel group study in a paediatric outpatient population (children and adolescents, ages 6-17). Patients 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, if 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 points on the CYBOCS total score which was significantly greater than the mean 3 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.

The safety of ZOLOFT use in children and adolescents, ages 6-18, for 52 weeks, was established in a flexible-dose, open extension study of 137 patients 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 this 52-week study ZOLOFT was well tolerated with an adverse event profile generally similar to that observed in the acute 12-week paediatric study. In the 12-week study, a marginally greater number of sertraline-treated patients (90%) experienced one or more adverse events (irrespective of causality), when compared to placebo (73%). The majority of adverse events in the sertraline group were classified as mild to moderate in severity.

Adults

The efficacy and safety of ZOLOFT in the treatment of OCD were established in three eight to twelve week controlled trials of non-depressed adult 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 behaviours performed in response to an obsession or in a stereotyped fashion, and are recognised by the person as excessive or unreasonable. In three double-blind, multicentre, 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.

Long-term treatment

In an open extension study of the 40-week continuation study mentioned above, 38 patients treated with sertraline received 2 full years of sertraline treatment. Sertraline responders treated for more than one year continued improvement during a second year of open treatment.

In addition, to assess the efficacy of sertraline in preventing relapse in patients who had achieved a sustained response during 52 weeks of single-blind sertraline therapy, a 28-week double-blind, placebo-controlled extension study of 223 patients demonstrated continued significant improvement in OCD symptoms when compared to placebo, with completion rates in the sertraline and placebo groups of 70% and 48%, respectively.

Panic Disorder

Adults

The efficacy and safety of ZOLOFT in the treatment of panic disorder in adults 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 120 mg (range: 25-200 mg) 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 25 mg/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 mg/day to 200 mg/day dose range investigated in the fixed dose studies. Efficacy beyond 12 weeks has not been assessed.

Social Phobia (Social Anxiety Disorder)

Adults

The effectiveness of ZOLOFT in the treatment of Social Phobia (Social Anxiety Disorder) was established in two multicentre placebo-controlled studies of adult outpatients who met DSM-IV criteria for Social Phobia (Social Anxiety Disorder). These criteria involve a marked and persistent fear or anxiety of behaving in an embarrassing or humiliating manner while under the gaze of other people in one or more social or performance situations. Exposure to the social or performance situation almost invariably provokes an immediate anxiety response. The patient recognises that the fear is excessive or unreasonable. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the patient's normal routine, occupational (academic) functioning, or social activities, or relationships, or there is marked distress about having the phobia. Performance anxiety, stage fright and shyness in social situations involving unfamiliar people should not be diagnosed as Social Phobia (Social Anxiety Disorder) unless the anxiety or avoidance leads to clinically significant impairment or marked distress.

A 12-week, multicentre, flexible-dose study compared ZOLOFT (50 mg/day to 200 mg/day) to placebo, in which ZOLOFT was initiated at 25 mg/day for the first week. Study outcome was assessed by (a) the Liebowitz Social Anxiety Scale (LSAS), and by (b) the proportion of responders as defined by the Clinical Global Impression of Improvement (CGI-I) criterion of CGI-I ≤ 2 (very much or much improved). ZOLOFT was significantly more effective than placebo as measured by the LSAS and the percentage of responders.

A 20-week, multicentre, flexible-dose study compared ZOLOFT (50 mg/day to 200 mg/day) to placebo. Study outcome was assessed by the (a) Duke Brief Social Phobia Scale (BSPS), (b) the Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS), and (c) the CGI-I responder criterion of ≤ 2. ZOLOFT was shown to be significantly more effective than placebo as measured by the BSPS total score and fear, avoidance and physiologic factor scores, as well as the FQ-SPS total score, and to have significantly more responders than placebo as defined by the CGI-I.

In a 24-week extension study of the 20-week study, patients meeting DSM-IV criteria for Social Phobia (Social Anxiety Disorder) who had responded to ZOLOFT during the 20-week placebo-controlled trial were randomised to continuation of ZOLOFT or to substitution of placebo for up to 24 weeks of observation for relapse. Patients receiving ZOLOFT continuation treatment experienced a significantly lower relapse rate than patients randomised to placebo substitution.

Cardiac Electrophysiology

In a dedicated thorough QTc study, conducted at steady-state at supratherapeutic exposures in healthy volunteers (treated with 400 mg/day, twice the maximum recommended daily dose), the upper bound of the

2-sided 90% CI for the time matched Least Square mean difference of QTcF between sertraline and placebo (11.666 msec) was greater than the predefined threshold of 10 msec at the 4-hour postdose time point. Exposure-response analysis indicated a slightly positive relationship between QTcF and sertraline plasma concentrations [0.036 msec/(ng/mL); $p < 0.0001$]. Based on the exposure-response model, the threshold for clinically significant prolongation of the QTcF (ie, for predicted 90% CI to exceed 10 msec) is at least 2.6-fold greater than the average C_{max} (86 ng/mL) following the highest recommended dose of sertraline (200 mg/day) (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 4.5 INTERACTIONS WITH OTHER MEDICINES and OTHER FORMS OF INTERACTIONS, 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 4.9 OVERDOSE).

Premenstrual Dysphoric Disorder (PMDD)

Adults

The effectiveness of ZOLOFT for the treatment of PMDD was established in two double-blind, parallel group, placebo-controlled flexible-dose trials (Studies 1 and 2) conducted over three menstrual cycles. Patients in Study 1 met DSM-III-R criteria for Late Luteal Phase Dysphoric Disorder (LLPDD), the clinical entity now referred to as PMDD in DSM-IV. Patients in Study 2 met DSM-IV criteria for PMDD. The DSM-IV criteria include markedly depressed mood, anxiety or tension, affective lability and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses. The disturbance markedly interferes with work or school or with usual social activities and relationships by prospective daily ratings during at least two consecutive symptomatic cycles. Efficacy was assessed with the Daily Record of Severity of Problems (DRSP), a patient-rated instrument that includes assessments for mood, physical symptoms, and other symptoms. Other efficacy assessments included the Hamilton Depression Rating Scale (HAMD-17), and the Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I) scores.

In Study 1, involving n=251 randomised patients, ZOLOFT treatment was initiated at 50 mg/day and administered daily throughout the menstrual cycle. In subsequent cycles, patients were dosed in the range of 50-150 mg/day on the basis of clinical response and tolerance.

In Study 2, involving n=281 randomised patients, ZOLOFT treatment was initiated at 50 mg/day in the late luteal phase (last 2 weeks) of each menstrual cycle and then discontinued at the onset of menses. In subsequent cycles, patients were dosed in the range of 50-100 mg/day in the luteal phase of each cycle, on the basis of clinical response and tolerance. Patients who were titrated to 100 mg/day received 50 mg/day for the first 3 days of the cycle, then 100 mg/day for the remainder of the cycle.

ZOLOFT administered continuously (Study 1) or intermittently (Study 2) was significantly more effective than placebo on all primary efficacy parameters as shown in Table 1.

Table 1: Change from baseline to endpoint [LS mean (+SE)] for primary efficacy parameters in ITT population, at statistically significant values (i.e. p < 0.005)

	Study 1		Study 2	
Primary Efficacy Parameters	Sertraline (N=104)	Placebo (N=106)	Sertraline (N=119)	Placebo (N=110)
DRSP Total Score	-25.1 (2.5)	-9.6 (2.4)	-24.7 (2.2)	-16.0 (2.4)
CGI-Severity Score	-1.6 (0.1)	-0.7 (0.1)	-1.6 (0.1)	-1.0 (0.2)
CGI-Improvement Score†	2.2 (0.1)	3.0 (0.1)	2.4 (0.1)	2.9 (0.1)
HAMD-17-item Score	-5.7 (0.6)	-3.4 (0.6)		

† CGI-I is endpoint score, as CGI-I question implicitly assesses change from baseline.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In man, following oral once-daily dosing over the range of 50 mg 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 was 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 mg 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 mg 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.

Distribution

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Metabolism

Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation.

Excretion

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 to 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 to 45% of the administered radioactivity was accounted for in faeces, including 12 to 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 to 9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Special Populations

Children and Adolescents

The pharmacokinetics of sertraline in paediatric OCD patients have been shown to be comparable to adults (although paediatric patients metabolise sertraline with slightly greater efficiency). However, lower doses may be advisable for paediatric patients, given their lower body weights (especially those patients aged 6 to 12 years), in order to avoid excessive plasma levels.

Adults

Sertraline plasma clearance were compared in male and female young subjects (18 to 45 years) and elderly subjects (≥ 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.

Hepatic Impairment

Sertraline is extensively metabolised by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis administered sertraline 50 mg/day for 21 days demonstrated a prolonged elimination half-life and approximately a three-fold greater AUC and C_{max} for sertraline and a two-fold greater AUC and C_{max} for the metabolite in comparison to normal subjects. Patients with moderate and severe hepatic impairment have not been studied. If ZOLOFT is administered to patients with hepatic impairment a lower or less frequent dose should be considered (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.2 DOSE AND METHOD OF ADMINISTRATION).

Renal Impairment

In patients with mild to moderate renal impairment (creatinine clearance 30 mL/min to 60 mL/min) or moderate to severe renal impairment (creatinine clearance 10 mL/min to 29 mL/min) administered sertraline 50 mg/day for 21 days multiple dose pharmacokinetic parameters (AUC_{0-24} or C_{max}) were not statistically significantly different compared with controls. This indicates that ZOLOFT dosing does not have to be adjusted based on degree of renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

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 mg/kg to 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 mg/kg to 40 mg/kg compared to placebo controls, this effect was not clearly drug related.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each ZOLOFT tablet contains the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate, hyprolose, sodium starch glycollate, magnesium stearate, OPADRY complete film coating system YS-1-7003 WHITE (ARTG PI No: 11956) and OPADRY complete film coating system YS-1-7006 CLEAR (ARTG PI No: 12789).

6.2 INCOMPATIBILITIES

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ZOLOFT 50 mg capsule-shaped tablets are packaged in PVC/Al blister packs of 7, 28 or 30 tablets.

ZOLOFT 100 mg capsule-shaped tablets are packaged in PVC/Al blister packs of 28 or 30 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 321601 - ZOLOFT sertraline (as hydrochloride) 50 mg tablet blister pack

AUST R 321602 – ZOLOFT sertraline (as hydrochloride) 100 mg tablet blister pack

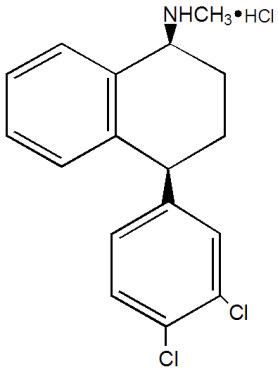
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical Structure



Chemical name:	(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride
Molecular formula:	$C_{17}H_{17}NCl_2.HCl$
Molecular weight:	342.7

CAS Number

79559-97-0.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

24/11/1993

10 DATE OF REVISION

30/06/2026

Summary Table of Changes

Section Changed	Summary of New Information
4.8	Addition of Multiple acyl-coenzyme A dehydrogenase deficiency (MADD)-like disorder as an unknown side effect.

ZOLOFT® is a Viatris company trade mark

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