SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

ZOLOFT® TABLETS 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sertraline hydrochloride equivalent to 50 mg sertraline.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

ZOLOFT TABLETS 50 mg: White, film-coated, capsule-shaped tablets, with “Pfizer” coded on the one side and the trade name abbreviation “ZLT” and “50” on the other side, with a functional score line between the two.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOLOFT is indicated in adults for:

- The treatment of major depressive disorders including single episodes and recurrent depression.
- The treatment of obsessive-compulsive disorder (OCD).
- The treatment of panic disorder, with or without agoraphobia.

ZOLOFT is indicated in:

- The treatment of children aged 13 – 17 with OCD.

Panic disorder

Panic disorder is characterised by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behaviour related to the attacks.

Panic disorder is characterised by recurrent unexpected panic attacks i.e. a discrete period of intense fear

or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, light-headed, or faint; derealisation (feelings of unreality) or depersonalisation (being detached from oneself); fear of losing control; fear of dying; paraesthesias (numbness or tingling sensations); chills or hot flushes.

The effectiveness of ZOLOFT in long-term use i.e. for more than 12 weeks, has not been systematically evaluated. Therefore, patients should be periodically re-evaluated regarding the long-term usefulness of the medicine (see section 4.2).

4.2 Posology and method of administration

Posology

ZOLOFT tablets should be given as a single daily dose with or without food.

Depression

The starting dose is 50 mg daily and the usual therapeutic dose in depression is 50 mg daily. In difficult to treat patients, the dose may be titrated up in 50 mg increments at 2 weekly intervals, to 150 mg – 200 mg.

Obsessive-compulsive disorder

Adults

The minimum effective dose in OCD is 50 mg daily and increases above 100 mg daily did not have any additional benefit. Full activity is usually seen after 2 – 4 weeks and even longer in OCD. Effect may however be seen within 7 days.

Paediatric obsessive-compulsive disorder (OCD)

The administration of ZOLOFT to paediatric OCD patients (aged 13 – 17) should commence at 50 mg/day. Subsequent doses may be increased in case of lack of response in 50 mg/day increments up to 200 mg as needed. However, the generally lower body weights of children compared to adults should be taken into consideration in advancing the dose from 50 mg, in order to avoid excessive dosing. Given the 24-hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

Panic disorder

For panic disorder, the minimum recommended dose of ZOLOFT is 50 mg/day. However, therapy for panic disorder should commence at 25 mg/day, increasing to 50 mg/day after one week. This dosage regimen has been demonstrated to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.

Special populations

Use in the elderly

No special precautions are required. The usual adult dosage is recommended.

Use in hepatic and renal impairment

See sections 4.3 and 4.4.

Discontinuation of treatment

If ZOLOFT therapy has to be discontinued, ZOLOFT should be tapered (see section 4.4).

Method of administration

For oral use.

4.3 Contraindications

- ZOLOFT is contraindicated in patients with known hypersensitivity to sertraline or any of the ingredients contained in ZOLOFT.
- The concomitant use of ZOLOFT with a monoamine oxidase inhibitor (MAOI), including the antibiotic linezolid, is contraindicated (see section 4.4).
- Concomitant use in patients taking pimozide is contraindicated (see section 4.5).
- Children < 18 years of age with both OCD and a major depressive disorder (see section 4.4).
- Use in hepatic or renal impairment (see section 4.4).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Serotonin Syndrome (SS)

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 ZOLOFT. The risk of SS or NMS with SSRIs is increased with concomitant use

of serotonergic medicines (including amphetamines, triptans and fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, meperidine, methadone and pentazocine), with medicines that impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. SS symptoms 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).

Monoamine oxidase inhibitors

Cases of serious reactions, sometimes fatal, have been reported in patients receiving ZOLOFT in combination with a MAOI, including selegiline, moclobemide, the antibiotic linezolid and methylene blue. Some cases presented with features resembling SS. Therefore, 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 elapse after discontinuing ZOLOFT treatment and starting a MAOI (see section 4.3).

Other serotonergic medicines

Co-administration of ZOLOFT with other medicines that enhance the effect of serotonergic neurotransmission, such as amphetamines, tryptophan and fentanyl, or 5-HT antagonists, or the herbal medicine St. John's Wort (*Hypericum perforatum*) should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction (see section 4.5).

QTc prolongation/Torsade de Pointes (TdP)

Cases of QTc prolongation and TdP have been reported during post-marketing use of ZOLOFT. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP. Therefore, ZOLOFT should be used with caution in patients with risk factors for QTc prolongation (see sections 4.5 and 5.1).

Switching from SSRIs, antidepressants or anti-obsessional medicines

There is limited controlled experience regarding the optimal timing of switching from other antidepressants or anti-obsessional medicines to ZOLOFT. Care and prudent medical judgement should be exercised when switching, particularly from long-acting medicines such as fluoxetine. The duration of a washout

period when switching from one SSRI to another has not been established.

Activation of mania/hypomania

Hypomania or mania may occur in patients treated with ZOLOFT.

Seizures

Seizures have been observed in patients using ZOLOFT. ZOLOFT should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. ZOLOFT should be discontinued in any patient who develops seizures.

Suicide/suicidal thoughts or clinical worsening

All patients treated with ZOLOFT, in particular younger patients and those at high risk, should be monitored appropriately and observed closely for clinical worsening and suicidality. Patients, their families, and their caregivers should be encouraged to be alert to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered, especially in depressed patients, and the smallest quantity of ZOLOFT, consistent with good patient management, should be provided to reduce the risk of overdose.

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with ZOLOFT should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania. Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing

ZOLOFT, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If a decision is made to discontinue treatment, ZOLOFT should be tapered (see section 4.2).

Abnormal bleeding/haemorrhage

There have been reports of bleeding abnormalities with SSRIs from ecchymosis and purpura to life-threatening haemorrhage. Caution is advised in patients taking SSRIs, particularly in concomitant use with medicines known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs [NSAIDs]) as well as in patients with a history of bleeding disorders (see section 4.5).

Hyponatraemia

Hyponatraemia may occur as a result of treatment with SSRIs such as ZOLOFT or serotonin norepinephrine inhibitors (SNRIs). 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 such as ZOLOFT. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk. Discontinuation of ZOLOFT 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 ZOLOFT. The mechanism leading to this risk is not fully understood.

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.

Use in hepatic impairment

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of ZOLOFT. The elimination half-life of ZOLOFT is prolonged. The use of ZOLOFT in patients with liver disease must be avoided (see section 4.3).

Use in renal impairment

In patients with mild to moderate renal impairment (creatinine clearance 30 – 60 mL/min) or severe renal impairment (creatinine clearance < 30 mL/min), multiple dose pharmacokinetics parameters (AUC or C_{max}) are modest. ZOLOFT should not be used in patients with renal impairment (see section 4.3).

Uricosuric effect

ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7 %. The clinical significance of this uricosuric effect is unknown.

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 medicine may need to be adjusted.

Laboratory tests

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

Angle-closure glaucoma

SSRIs including ZOLOFT 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. ZOLOFT should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Weight loss

Significant weight loss may be an undesirable result of treatment with ZOLOFT for some patients,

approximately 0,5 – 1,0 kg weight loss.

Paediatric population

The safety and efficacy of ZOLOFT have been established in paediatric obsessive-compulsive disorder (OCD) patients aged 13 – 17. Safety and efficacy in the paediatric population other than paediatric patients with OCD have not been established. In clinical trials in major depressive disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm (see section 4.3).

Withdrawal symptoms

Abrupt discontinuation of ZOLOFT may lead to withdrawal symptoms which include dizziness, sweating, nausea, insomnia, tremor, confusion, sensory disturbances, agitation and anxiety.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOI)

The concomitant use of ZOLOFT with a MAOI is contraindicated (see sections 4.3 and 4.4).

Pimozide

Increased pimozide levels have been demonstrated with ZOLOFT co-administration but were not associated with any changes in electrocardiogram (ECG). While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of ZOLOFT and pimozide is contraindicated (see section 4.3).

Medicines that prolong the QTc interval

The risk of QTc prolongation and/or ventricular dysrhythmias (e.g. TdP) is increased with concomitant use of other medicines that prolong the QTc interval (e.g. some antipsychotics and antibiotics) (see sections 4.4 and 5.1).

CNS depressants and alcohol

Co-administration of ZOLOFT (sertraline 200 mg daily) did not potentiate the effects of alcohol, carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects. However, the concomitant use of ZOLOFT and alcohol in depressed patients is not recommended.

Lithium

It is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy, so that

appropriate adjustments to the lithium dose may be made if necessary. Co-administration with lithium may lead to a higher incidence of 5HT-associated side effects, resulting in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. Therefore, caution is recommended when co-administering ZOLOFT with medicines such as lithium, which may act via serotonergic mechanisms and patients should be appropriately monitored.

Phenytoin

Increased phenytoin concentrations may occur when ZOLOFT and phenytoin are used concomitantly, especially in patients with other medical conditions and/or those receiving multiple concomitant medications. Plasma phenytoin concentrations should be monitored when ZOLOFT and phenytoin are used concomitantly with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of plasma levels of sertraline in ZOLOFT.

Sumatriptan

There have been post-marketing reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety, and agitation following the use of ZOLOFT and sumatriptan. If concomitant treatment with ZOLOFT and sumatriptan is clinically warranted, appropriate observation of the patient is advised (see section 4.4 and Other serotonergic medicines below).

Other serotonergic medicines

Co-administration of ZOLOFT with other medicines which enhance the effect of serotonergic neurotransmission, such as tryptophan and fentanyl, 5-HT antagonists, or the herbal medicine St. John's Wort (*Hypericum perforatum*) should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction (see section 4.4).

Protein-bound medicines

ZOLOFT 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 as in ZOLOFT do not alter the plasma protein binding of two other highly protein-bound medicines, viz. warfarin and propranolol. However, in interaction studies with diazepam, tolbutamide and warfarin respectively, ZOLOFT had no significant effects on the protein binding of the substrate (see Warfarin and Other medicine interactions).

Warfarin

Co-administration of ZOLOFT 200 mg daily with warfarin resulted in a small but statistically significant

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

Other medicine interactions

Co-administration of ZOLOFT 200 mg daily with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters.

Co-administration with cimetidine caused a substantial decrease in ZOLOFT clearance. The clinical significance of these changes is unknown.

ZOLOFT has no effect on the beta-adrenergic blocking ability of atenolol. No interaction of ZOLOFT 200 mg daily was observed with glibenclamide or digoxin.

Electroconvulsive therapy (ECT)

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

Medicines metabolised by cytochrome P450 (CYP) 2D6

There is variability among antidepressants in the extent of clinically important inhibition of the medicine metabolising isoenzyme cytochrome (CYP) 2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered medicine. CYP 2D6 substrates with a narrow therapeutic index include tricyclic antidepressants (TCAs) and class 1C anti-dysrhythmics such as propafenone and flecainide. In formal interaction studies, chronic dosing with ZOLOFT 50 mg daily showed minimal elevation of steady state desipramine plasma levels (a marker of CYP 2D6 isoenzyme activity).

Medicines metabolised by other CYP enzymes (CYP 3A3/4, CYP 2C9, CYP 2C19, CYP 1A2)

CYP 3A3/4

Chronic administration of ZOLOFT 200 mg daily does not inhibit the CYP 3A3/4 mediated 6-β hydroxylation of endogenous cortisol or the metabolism of carbamazepine. In addition, the chronic administration of ZOLOFT 50 mg daily does not inhibit the CYP 3A3/4 mediated metabolism of alprazolam. The results of these studies suggest that ZOLOFT is not a clinically relevant inhibitor of CYP 3A3/4.

CYP 2C9

The apparent lack of clinically significant effects of the chronic administration of ZOLOFT 200 mg daily on plasma concentrations of tolbutamide, phenytoin and warfarin suggest that ZOLOFT is not a clinically

relevant inhibitor of CYP 2C9 (see Other medicine interactions, Phenytoin and Warfarin).

CYP 2C19

The apparent lack of clinically significant effects of the chronic administration of ZOLOFT 200 mg daily on plasma concentrations of diazepam suggests that ZOLOFT is not a clinically relevant inhibitor of CYP 2C19 (see Other medicine interactions).

CYP 1A2

In vitro studies indicate that ZOLOFT has little or no potential to inhibit CYP 1A2.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should employ an adequate method of contraception if taking ZOLOFT (see section 4.3).

Pregnancy

The safety of ZOLOFT during pregnancy and lactation has not been established.

Breastfeeding

Women using ZOLOFT should not breastfeed their infants.

Fertility

There is no clinical trial data on fertility. In animal studies, no effect on fertility parameters was observed.

4.7 Effects on ability to drive and use machines

ZOLOFT does not cause sedation and does not interfere with psychomotor performance but may cause hypomania.

Patients should be cautioned when driving a car or operating machinery until they know how ZOLOFT affects them.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The adverse event terms in clinical studies were categorised utilising the incidence rate as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to <

1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

MedDRA System organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Common	Pharyngitis
	Uncommon	Upper respiratory tract infection, rhinitis
	Rare	Diverticulitis, gastroenteritis, otitis media
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Rare	Neoplasm
Blood and lymphatic system disorders	Rare	Lymphadenopathy
Immune system disorders	Rare	Allergic reaction, allergy
Metabolism and nutrition disorders	Common	Anorexia, decreased appetite
	Rare	Hypercholesterolaemia
Psychiatric disorders	Very common	Insomnia
	Common	Depersonalisation, nervousness, suicidal ideation/behaviour, suicide attempts
	Uncommon	Apathy, abnormal thinking
	Rare	Paroniria, psychosis, conversion disorder, medicine dependence, paranoia, sleep walking, premature ejaculation
Nervous system disorders	Very common	Dizziness, somnolence
	Common	Tremor, dysgeusia, disturbance in attention
	Uncommon	Abnormal coordination, amnesia, speech disorder, postural dizziness
	Rare	Choreoathetosis, dyskinesia, hyperaesthesia, sensory disturbance
	Not known	Psychomotor restlessness (see section 4.4)
Eye disorders	Common	Abnormal vision, visual disturbance

	Rare	Glaucoma, lacrimal disorder, scotoma, diplopia, photophobia, hyphaemia
	Not known	Unequal pupils
Ear and labyrinth disorders	Uncommon	Ear pain
Cardiac disorders	Rare	Myocardial infarction, bradycardia, cardiac disorder
Vascular disorders	Uncommon	Flushing
	Rare	Peripheral ischaemia, haematuria, abnormal bleeding (such as gastrointestinal bleeding)
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
	Rare	Laryngospasm, hyperventilation, hypoventilation, stridor, dysphonia, hiccups
	Not known	Interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhoea/loose stools, dry mouth, nausea
	Common	Dyspepsia, flatulence
	Uncommon	Oesophagitis, dysphagia, haemorrhoids, salivary hypersecretion, tongue disorder, eructation
	Rare	Melaena, haematochezia, stomatitis, tongue ulceration, tooth disorder, glossitis, mouth ulceration
Hepatobiliary disorders	Rare	Abnormal hepatic function, serious liver events (including hepatitis, jaundice and hepatic failure)
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Uncommon	Cold sweat, dry skin
	Rare	Dermatitis, bullous dermatitis, follicular rash, abnormal hair texture, abnormal skin odour
Musculoskeletal and connective	Common	Myalgia

tissue disorders	Uncommon	Muscle cramps, osteoarthritis, muscular weakness, back pain, muscle twitching
	Rare	Bone disorder
Renal and urinary disorders	Uncommon	Nocturia, polyuria, pollakiuria, micturition disorder
	Rare	Oliguria, urinary hesitation
Reproductive system and breast disorders	Very common	Ejaculation failure
	Common	Ejaculation disorder, erectile dysfunction, sexual dysfunction
	Uncommon	Vaginal haemorrhage, female sexual dysfunction
	Rare	Menorrhagia, atrophic vulvovaginitis, balanoposthitis, genital discharge
General disorders and administration site conditions	Uncommon	Chills, thirst
	Rare	Hernia, decreased medicine tolerance
Investigations	Rare	Abnormal semen
Injury, poisoning and procedural complications	Rare	Injury
Surgical and medical procedures	Rare	Vasodilation procedure
Other	Rare	Symptoms following the discontinuation of ZOLOFT have been reported and included agitation, anxiety, dizziness, headache, nausea, paraesthesia

Post-marketing side effects

MedDRA System organ class	**Adverse reactions**
Blood and lymphatic system disorders	Thrombocytopenia, leukopenia, abnormal platelet function test
Immune system disorders	Hypersensitivity, anaphylactoid reaction
Endocrine disorders	Inappropriate antidiuretic hormone secretion, hyperprolactinaemia, hypothyroidism
Metabolism and nutrition disorders	Increased appetite, diabetes mellitus, hyponatremia, hypoglycaemia, hyperglycaemia
Psychiatric disorders	Depressive symptoms, depression, anxiety, agitation, bruxism, nightmare, decreased libido, hallucination, aggression, confusional state, euphoric mood, psychotic disorder
Nervous system disorders	Headache, paraesthesia, syncope, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, dystonia, teeth grinding or gait abnormalities), involuntary muscle contractions, hypoaesthesia, hyperkinesia, migraine. Also reported were signs and symptoms associated with Serotonin Syndrome or Neuroleptic Malignant Syndrome: In some cases associated with concomitant use of serotonergic medicines that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity, and tachycardia, coma, convulsion, dystonia, akathisia
Eye disorders	Visual impairment, mydriasis, periorbital oedema
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Palpitations, tachycardia, Torsade de Pointes, QTc prolongation, increased blood cholesterol
Vascular disorders	Hot flush, haemorrhage, hypertension, cerebral vasoconstriction (including reversible cerebral

	vasoconstriction syndrome and Call-Fleming syndrome)
Respiratory, thoracic and mediastinal disorders	Yawning, bronchospasm, epistaxis
Gastrointestinal disorders	Vomiting, constipation, abdominal pain, gastrointestinal haemorrhage, pancreatitis
Hepatobiliary disorders	Increased alanine aminotransferase, increased aspartate aminotransferase, liver injury
Skin and subcutaneous tissue disorders	Rash, urticaria, purpura, pruritus, alopecia, rare reports of severe cutaneous adverse reactions (SCAR) e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, exfoliative rash, photosensitivity skin reaction
Musculoskeletal and connective tissue disorders	Arthralgia, muscle spasms, rhabdomyolysis, trismus
Renal and urinary disorders	Urinary retention, haematuria, urinary incontinence, enuresis
Reproductive system and breast disorders	Irregular menstruation, priapism, galactorrhoea, gynaecomastia
General disorders and administration site conditions	Chest pain, malaise, pyrexia, asthenia, fatigue, gait disturbance, peripheral oedema, face oedema, medicine withdrawal syndrome
Investigations	Increased weight, decreased weight, abnormal clinical laboratory results
Injury, poisoning and procedural complications	Fracture

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting**

Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

On the evidence available, ZOLOFT has a wide margin of safety in overdose. Deaths have been reported involving overdoses of ZOLOFT, primarily in combination with other medicines and/or alcohol. Therefore, any overdosage should be treated aggressively.

Symptoms of overdose include serotonin-mediated side effects such as electrocardiogram QT prolonged, TdP (see sections 4.4, 4.5 and 5.1), somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness. Less frequently reported was coma.

No specific therapy is recommended and there are no specific antidotes to ZOLOFT.

Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, a cathartic, should be considered for the induction of emesis or lavage in treating overdosage. Induction of emesis is not recommended. Monitoring of cardiac and vital signs is recommended, along with general symptomatic and supportive measures. Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants)

Mechanism of action

Sertraline is a selective serotonin re-uptake inhibitor. The mechanism of action of sertraline is presumed to be linked to the inhibition of central nervous system neuronal uptake of serotonin (5HT). Sertraline blocks the uptake of serotonin into human platelets. Sertraline has been shown to be a specific inhibitor of neuronal serotonin re-uptake and has only very weak effects on the norepinephrine (noradrenaline) and dopamine neuronal re-uptake.

Sertraline does not enhance catecholaminergic activity and it has no affinity for cholinergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), dopaminergic, adrenergic ($alpha_1$, $alpha_2$, beta) histaminergic, GABA or benzodiazepine receptors.

The chronic administration of sertraline in animals was associated with downregulation of brain norepinephrine (noradrenaline) receptors.

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 post dose time point. Exposure-response analysis indicated a relationship between QTcF and sertraline plasma concentrations [0,036 msec/(ng/mL); p < 0,0001] (see sections 4.4, 4.5, 4.8 and 4.9).

5.2 Pharmacokinetic properties

Sertraline exhibits dose proportional pharmacokinetics over the range 50 – 200 mg. After oral administration over the range of 50 to 200 mg once daily for 14 days, mean peak blood levels were reached at 4,5 – 8,4 hours post dose. The average terminal plasma half-life is about 26 hours. Steady state plasma levels are reached after approximately one week of once daily dosing. Approximately 98 % of the circulating medicine is bound to plasma proteins. Consistent with the terminal elimination half-life, there is approximately two-fold accumulation with repeated dosing as compared to a single dose.

Sertraline undergoes extensive first pass hepatic metabolism. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown the principal metabolite, N-desmethylsertraline, to have significantly less clinical activity. Both sertraline and N-desmethylsertraline are extensively metabolised with only a small amount (< 0,2 %) of unchanged sertraline excreted in urine. About 40 – 45 % of the dose administered radioactively was recovered in the urine and a similar amount in the faeces, including 12 – 14 % unchanged sertraline. The terminal elimination half-life of N-desmethylsertraline is approximately 62 to 104 hours. Desmethylsertraline exhibits time related dose dependent increases in AUC, C_{max} and C_{min} with a 5 to 9-fold increase in their parameters between day 1 and day 14.

Protein binding

Sertraline is highly bound to serum proteins (98 %) in the range of 20 to 500 ng/mL.

Age

Sertraline plasma clearance in elderly patients is approximately 40 % lower than in younger (25 to 32-

year-old) individuals. Steady state, therefore, should be achieved after 2 to 3 weeks in older patients. There is a decreased clearance of desmethylsertraline in older males, but not in older females.

The pharmacokinetics profile in adolescents is not significantly different from that in adults between 18 and 65 years. The mean half-life of sertraline for young men and women ranges from 22 – 36 hours. The pharmacokinetics of sertraline in paediatric obsessive-compulsive disorder (OCD) patients have been shown to be comparable to adults (although paediatric patients metabolise sertraline faster). However, lower doses may be advisable in paediatric patients given their lower body weights (especially 6 – 12 years), in order to avoid excessive plasma levels.

Liver disease

The metabolism of sertraline is delayed in patients with impaired liver function (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Calcium hydrogen phosphate

Hydroxypropylcellulose

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate

Tablet coat

Methylhydroxypropyl cellulose (E464)

Polyethylene glycol

Polysorbate

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

ZOLOFT TABLETS 50 mg: Opaque PVC/aluminium blister packs containing 30, 60, 90, 120, 240 and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

Tel.: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

ZOLOFT TABLETS 50 mg: 32/1.2/0381

9. DATE OF FIRST AUTHORISATION

20 April 2000

10. DATE OF REVISION OF THE TEXT

08 February 2021

BOTSWANA: S2

Reg. No.: BOT9800298

NAMIBIA: NS3

Reg. No.: 04/1.2/1240