ZOLOFT®

1. Name of Medicinal Product

ZOLOFT®

2. Qualitative and Quantitative Composition

ZOLOFT® is available as film-coated tablets for oral administration containing sertraline hydrochloride equivalent to 50 mg sertraline.

3. Pharmaceutical Form

Film-coated tablets.

4. Clinical Particulars

4.1 Therapeutic Indications

Sertraline is indicated for the treatment of symptoms of depression, including depression accompanied by symptoms of anxiety, in patients with or without a history of mania. Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes.

Sertraline is also indicated for the treatment of obsessive compulsive disorder (OCD). Following initial response, sertraline has been associated with sustained efficacy, safety and tolerability in up to 2 years of treatment of OCD.

Sertraline is indicated for the treatment of panic disorder, with or without agoraphobia.

Sertraline is indicated for the treatment of post-traumatic stress disorder (PTSD).

Sertraline is indicated for the treatment of social phobia (social anxiety disorder).

Sertraline is indicated for the treatment of pre-menstrual dysphoric disorder (PMDD).

Sertraline is not indicated for use in children and adolescents under 18 years of age (see section **4.4 – Special Warnings and Precautions for Use**).

4.2 Posology and Method of Administration

Sertraline should be administered once daily, either in the morning or evening. Sertraline tablets can be administered with or without food.

Initial Treatment

Depression and OCD – Sertraline treatment should be administered at a dose of 50 mg/day.

Panic Disorder, PTSD and Social Phobia – Therapy should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early-treatment-emergent side effects characteristic of panic disorder.

Pre-menstrual Dysphoric Disorder – Sertraline treatment should be initiated at a dose of 50 mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.

Titration

Depression, OCD, Panic Disorder, PTSD, and Social Phobia – Patients not responding to a 50 mg dose may benefit from dose increases. Dose changes should be made at intervals of at least one week, up to a maximum of 200 mg/day. Changes in dose should not be made more frequently than once per week given the 24-hour elimination half-life of sertraline.

The onset of therapeutic effect may be seen within 7 days. However, longer periods are usually necessary to demonstrate therapeutic response, especially in OCD.

Pre-menstrual Dysphoric Disorder – 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 utilized at the beginning of each luteal phase dosing period.

Maintenance – Dosage during long-term therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response.

Use in the Elderly – The same dose range as in younger patients may be used in the elderly. Over 700 elderly patients (>65 years) have participated in clinical studies that demonstrated the efficacy of sertraline in this patient population. The pattern and incidence of adverse reactions in the elderly were similar to that in younger patients.

Use in Hepatic Insufficiency – The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment (see section **4.4 – Special Warnings and Precautions for Use**).

Use in Renal Insufficiency – Sertraline is extensively metabolized. Excretion of unchanged drug in urine is a minor route of elimination. As expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment (see section **4.4 – Special Warnings and Precautions for Use**).

Discontinuation

Patients currently taking sertraline should not be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue, a gradual reduction in the dose rather than an abrupt cessation is recommended.

4.3 Contraindications

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

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see section **4.4 – Special Warnings and Precautions for Use**).

Concomitant use in patients taking pimozide is contraindicated (see section **4.5 – Interaction with Other Medicinal Products and Other Forms of Interaction**).

4.4 Special Warnings and Precautions for Use

Serotonin 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, meperidine, 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, diarrhea). 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**).

Monoamine Oxidase Inhibitors – Cases of serious reactions, sometimes fatal, have been reported in patients receiving sertraline in combination with a MAOI, including the selective MAOI selegiline, the reversible MAOI 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 SS, the symptoms of which include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. Therefore, sertraline 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 sertraline treatment before starting a MAOI (see section **4.3 – Contraindications**).

Other Serotonergic Drugs – Co-administration of sertraline with other drugs that enhance the effects of serotonergic neurotransmission, such as amphetamines, tryptophan or fenfluramine, and fentanyl, 5-HT agonists, 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.

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 – Interaction with Other Medicinal Products and Other Forms of Interaction** and **5.1 – Pharmacodynamic Properties**).

Switching from Selective Serotonin Reuptake Inhibitors, Antidepressants or Anti-obsessional Drugs – There is limited controlled experience regarding the optimal timing of switching from SSRIs, antidepressants or anti-obsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents, such as fluoxetine. The duration of a washout period for switching from one SSRI to another has not been established.

Activation of Mania/Hypomania – During pre-marketing testing, hypomania or mania occurred in approximately 0.4% of sertraline-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder treated with other marketed antidepressant and anti-obsessional drugs.

Seizures – Seizures are a potential risk with antidepressant and anti-obsessional drugs. Seizures were reported in approximately 0.08% of patients treated with sertraline in the development program for depression. No seizures were reported in patients treated with sertraline in the development program for panic. During the development program for OCD, four out of approximately 1,800 patients exposed to sertraline experienced seizures (approximately 0.2%). Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. In all these cases, the relationship with sertraline therapy was uncertain. Since sertraline has not been evaluated in patients with a seizure disorder, it should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

Suicide/Suicidal Thoughts or Clinical Worsening – All patients treated with sertraline, in particular 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 behavior or thoughts and unusual changes in behavior 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 drug, consistent with good patient management, should be provided to reduce the risk of overdose.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young

adults (aged 18 to 24 years) with major depression and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults aged 65 years and older.

Sexual Dysfunction – Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction (see section **4.8 – Undesirable Effects**). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

Abnormal Bleeding/Hemorrhage – There have been reports of bleeding abnormalities with SSRIs from ecchymoses and purpura to life-threatening hemorrhage. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs 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 – Interaction with Other Medicinal Products and Other Forms of Interaction**).

Hyponatremia – Hyponatremia may occur as a result of treatment with SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) including sertraline. In many cases, hyponatremia 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 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk (see section **4.2 – Posology and Method of Administration:** Use in the Elderly). Discontinuation of sertraline should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia 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.

Because of the well-established comorbidity between OCD and depression, panic disorder and depression, PTSD and depression, and social phobia and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD, panic disorder, PTSD or social phobia.

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.

Use in Hepatic Insufficiency – Sertraline is extensively metabolized by the liver. A multiple-dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and approximately three-fold greater AUC and C_{max} 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. A lower or less frequent dose should be used in patients with hepatic impairment.

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

Diabetes/Loss of Glycemic Control – Cases of new-onset diabetes mellitus have been reported in patients receiving SSRIs including sertraline. Loss of glycemic control including both hyperglycemia and hypoglycemia 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 glycemic control carefully monitored since their dosage of insulin and/or concomitant oral hypoglycemic drug may need to be adjusted.

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.

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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Monoamine Oxidase Inhibitors – See sections **4.3 – Contraindications** and **4.4** – **Special Warnings and Precautions for Use**.

Pimozide – Increased pimozide levels have been demonstrated in a study of a single low-dose pimozide (2 mg) with sertraline co-administration. These increased levels were not associated with any changes in electrocardiogram (EKG). While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated.

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** and **5.1 – Pharmacodynamic Properties**).

CNS Depressants and Alcohol – The co-administration of 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 sertraline and alcohol is not recommended.

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

Phenytoin – A placebo-controlled trial in normal volunteers suggests that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, it is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels.

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).

Other Serotonergic Drugs – See section **4.4 – Special Warnings and Precautions for Use**: Serotonin Syndrome, Monoamine Oxidase Inhibitors, and Other Serotonergic Drugs.

Protein-Bound Drugs – Since sertraline is bound to plasma proteins, the potential of sertraline to interact with other plasma protein-bound drugs should be borne in mind. However, in three formal interaction studies with diazepam, tolbutamide and warfarin, respectively, sertraline was not shown to have significant effects on the protein binding of the substrate (see subsections Warfarin and Other Drug Interactions).

Warfarin – Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Other Drug Interactions – Formal drug interaction studies have been performed with sertraline. Co-administration of sertraline 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 sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction of sertraline 200 mg daily was observed with glibenclamide or digoxin.

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

Drugs Metabolized by Cytochrome P450 2D6 – There is variability among antidepressants in the extent to which they inhibit the activity of isozyme cytochrome P450 (CYP) 2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered drug. CYP 2D6 substrates with a narrow therapeutic index include tricyclic antidepressants (TCAs) and class 1C antiarrhythmics, such as propafenone and flecainide. In formal interaction studies, chronic dosing with sertraline 50 mg daily showed minimal elevation (mean 23% to 37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isoenzyme activity).

Drugs Metabolized by Other CYP Enzymes (CYP 3A3/4, CYP 2C9, CYP 2C19, CYP 1A2)
CYP 3A3/4: *In vivo* interaction studies have demonstrated that chronic administration of sertraline 200 mg daily does not inhibit the CYP 3A3/4-mediated 6-ß hydroxylation of endogenous cortisol or the metabolism of carbamazepine or terfenadine. In addition, the chronic administration of sertraline 50 mg daily does not inhibit the CYP 3A3/4-mediated metabolism of alprazolam. The data suggest that sertraline is not a clinically relevant inhibitor of CYP 3A3/4.

Co-administration of sertraline with metamizole, which is an inducer of metabolizing enzymes including CYP2B6 and CYP3A4 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 200 mg daily on plasma concentrations of tolbutamide, phenytoin and warfarin suggests that sertraline is not a clinically relevant inhibitor of CYP 2C9 (see subsections Other Drug Interactions, Phenytoin, and Warfarin).

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

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

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 times and 10 times the maximum daily human mg/kg dose, respectively. There was no evidence of teratogenicity at any dose level. At the dose level corresponding to approximately 2.5 to 10 times the maximum daily human mg/kg dose, however, sertraline was associated with delayed ossification in fetuses, probably secondary to effects on the dams.

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

There was decreased neonatal survival following maternal administration of sertraline at doses approximately five times the maximum daily human mg/kg dose. Similar effects on neonatal survival have been described for other antidepressant drugs. The clinical significance of these effects is unknown.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sertraline should be used during pregnancy only if the perceived benefits outweigh the risks.

If sertraline is used during pregnancy and/or lactation, the physician should be aware that symptoms, including those compatible with withdrawal reactions, have been reported in some neonates whose mothers had been on SSRI antidepressants, including sertraline.

Women of childbearing potential should employ an adequate method of contraception if taking sertraline.

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 1,000 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”.

Lactation

Isolated studies in small numbers of nursing mothers and their infants indicated negligible or undetectable levels of sertraline in infant serum, although levels in breast milk were more concentrated than in maternal serum. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefits outweigh the risks.

Fertility

There is no clinical trial data on fertility. In animal studies, no effect on fertility parameters was observed (see also section **5.3** – **Preclinical Safety Data**).

4.7 Effects on Ability to Drive and Use Machines

Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However, as psychotropic drugs may impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, the patient should be cautioned accordingly.

4.8 Undesirable Effects

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

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	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)	Frequency Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Thrombocytopenia*§, Leukopenia*§, Platelet function test abnormal*§	
Immune system disorders			Hypersensitivity*	Anaphylactoid reaction*§	
Endocrine disorders			Hypothyroidism*	Inappropriate antidiuretic hormone secretion*§, Hyperprolactinemia*§	
Metabolism and nutrition disorders		Decreased appetite, Increased appetite*		Diabetes mellitus*, Hyponatremia*§, Hypoglycemia*, Hyperglycemia*§	
Psychiatric disorders	Insomnia	Depressive symptoms*, Anxiety*, Agitation*, Bruxism*, Nightmare*, Libido decreased*	Hallucination*, Aggression*, Confusional state*, Euphoric mood*	Psychotic disorder*	
Nervous system disorders	Somnolence, Dizziness, Headache*	Hypertonia*, Tremor, Paresthesia*	Syncope*, Extrapyramidal disorder*, Muscle contractions involuntary*, Hypoesthesia*, Hyperkinesia*, Migraine*	Serotonin syndrome*§, Coma*, Convulsion*§, Dystonia*§, Akathisia*	
Eye disorders		Visual impairment*	Mydriasis*, Periorbital edema*		
Ear and labyrinth disorders		Tinnitus*			
Cardiac disorders		Palpitations*	Tachycardia*	Torsade de pointes*§ (see sections 4.4, 4.5 and 5.1), Electrocardiogram QT prolonged* (see sections 4.4, 4.5 and	

System Organ Class	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)	Frequency Not Known (cannot be estimated from the available data)
				5.1), Blood cholesterol increased*§	
Vascular disorders		Hot flush*	Hemorrhage*, Hypertension*	Cerebral vasoconstriction*§ (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome)	
Respiratory, thoracic and mediastinal disorders		Yawning*	Bronchospasm*, Epistaxis*	Eosinophilic pneumonia*§	
Gastrointestinal disorders	Diarrhea, Nausea	Vomiting*, Constipation*, Abdominal pain*, Dry mouth, Dyspepsia	Gastrointestinal hemorrhage*	Pancreatitis*§	Microscopic colitis*
Hepatobiliary disorders			Alanine aminotransferase increased*, Aspartate aminotransferase increased*	Liver injury*§	
Skin and subcutaneous tissue disorders		Rash*, Hyperhidrosis	Urticaria*, Purpura*, Pruritus*, Alopecia*	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*, Hematuria*, Urinary incontinence*	Enuresis*§	
Reproductive system and breast disorders	Ejaculation disorder	Sexual dysfunction (see section 4.4), Menstruation irregular*		Priapism*, Galactorrhea*, Gynecomastia*	
General disorders and administration site conditions	Fatigue*	Chest pain*, Malaise*, Pyrexia*, Asthenia*	Gait disturbance*, Edema peripheral*	Face edema*, Drug withdrawal syndrome*§	

System Organ Class	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)	Frequency Not Known (cannot be estimated from the available data)
Investigations		Weight increased*	Weight decreased*	Laboratory test abnormal*	
Injury, poisoning and procedural complications				Fracture*	

*ADR identified post-marketing.
§ – ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using "The Rule of 3".
ADR = adverse drug reaction; SOC = System Organ Class; CIOMS = Council for International Organization of Medical Sciences

4.9 Overdose

Sertraline has a margin of safety dependent on patient population and/or concomitant medications. Deaths have been reported involving overdoses of sertraline, alone or in combination with other drugs 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 – Special Warnings and Precautions for Use**, **4.5 – Interaction with Other Medicinal Products and Other Forms of Interaction** and **5.1 – Pharmacodynamic Properties**) somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness. Less frequently reported was coma.

There are no specific antidotes to sertraline. Establish and maintain an airway and ensure adequate oxygenation and ventilation, if necessary. Activated charcoal, which may be used with a cathartic, may be as or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended. Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) reuptake *in vitro*, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, gamma-aminobutyric acid (GABA) or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of brain

norepinephrine receptors as observed with other clinically effective antidepressants and anti-obsessional drugs.

No weight gain was observed in controlled clinical trials with sertraline treatment for depression or OCD; some patients may experience a reduction in body weight with sertraline.

Sertraline has not demonstrated potential for abuse. In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria and abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforcer in rhesus monkeys trained to self-administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

Clinical Trials

Major Depressive Disorder

A study was conducted that involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50 mg/day to 200 mg/day. These patients (n = 295) were randomized to continuation for 44 weeks on double-blind sertraline 50 mg/day to 200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo. The mean dose for completers was 70 mg/day.

Obsessive-compulsive Disorder

In a long-term study, patients meeting DSM-III-R criteria for OCD who had responded during a 52-week single-blind trial on sertraline 50 mg/day to 200 mg/day (n = 224) were randomized to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Patients receiving continued sertraline treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Panic Disorder

In a long-term study, patients meeting DSM-III-R criteria for panic disorder who had responded during a 52-week open trial on sertraline 50 mg/day to 200 mg/day (n = 183) were randomized to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Patients receiving continued sertraline treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Post-traumatic Stress Disorder

In a long-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on sertraline 50 mg/day to 200 mg/day (n = 96) were randomized to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for relapse. Patients receiving continued sertraline treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Social Phobia (Social Anxiety Disorder)

In a social phobia relapse prevention study, patients who were responders at the end of a 20 week, multicenter, flexible-dose study that compared sertraline (50 mg/day to 200 mg/day) to placebo, were re-randomized for an additional 24 weeks to either sertraline continuation treatment (within 50 mg/day to 200 mg/day) or placebo substitution, while placebo responders remained on placebo. Patients receiving sertraline continuation treatment experienced a statistically significantly lower relapse rate over this 24-week study than patients randomized to placebo substitution treatment.

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 different 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 (i.e., 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 – Interaction with Other Medicinal Products and Other Forms of Interaction**, **4.8 – Undesirable Effects** and **4.9 – Overdose**).

5.2 Pharmacokinetic Properties

Sertraline exhibits dose-proportional pharmacokinetics over the range of 50 mg to 200 mg. In man, following oral once-daily dosing over the range of 50 mg to 200 mg for 14 days, peak plasma concentrations (C_{max}) of sertraline occur at about 4.5 to 8.4 hours post-dosing. The pharmacokinetic profile in either adolescents or the elderly is not significantly different from that in adults between 18 and 65 years. The mean half-life of sertraline for young and elderly men and women ranges from 22 to 36 hours. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation up to steady-state concentrations, which are achieved after one week of once-daily dosing. Approximately 98% of the circulating drug is bound to plasma proteins. Animal studies indicate that sertraline has a large apparent volume of distribution.

Sertraline undergoes extensive first-pass hepatic metabolism. The principal metabolite in plasma, N-desmethylsertraline, is substantially less active (about 20 times) than sertraline *in vitro* and there is no evidence of activity in *in vivo* models of depression. The half-life of N-desmethylsertraline is in the range of 62 to 104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in feces and urine in equal amounts. Only a small amount (<0.2%) of unchanged sertraline is excreted in urine.

Food does not significantly change the bioavailability of sertraline tablets.

5.3 Preclinical Safety Data

Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective. Sertraline has also been shown to be devoid of mutagenic effects.

Juvenile Animal Studies
In a juvenile toxicology study in Sprague-Dawley rats, dose levels of 0, 10, 40 or 80 mg/kg/day of sertraline were administered orally to male and female rats on post-natal Days 21 through 56, with a non-dosing recovery phase up to post-natal Day 196. The administration of 80 mg/kg of sertraline to males and females on post-natal Days 21 to 56 resulted in dehydration, chromorhinorrhea and reduced average body weight gain. In addition, rales, hunched posture and reduced food consumption also occurred in male rats given 80 mg/kg/day. Delays in sexual maturation occurred in males (80 mg/kg/day) and females ($\geqslant$10 mg/kg/day), but despite this finding there were no sertraline-related effects on any of the male (organ weights, mating and fertility, sperm motility or sperm concentration) or female (estrous cycling, mating and fertility, or ovarian and uterine parameters) reproductive endpoints that were assessed. There were no sertraline-related effects on any behavior parameter (learning and memory, auditory startle response, and locomotor activity) in males, while a decrease in auditory startle response occurred in females at 40 and 80 mg/kg/day. There were no sertraline-related effects on male or female femur lengths, brain weights, gross necropsy or microscopic observations at any dose level. In juvenile males, the no-observed-adverse-effect level (NOAEL) for general toxicity was 40 mg/kg/day (correlating to a C_{max} of 262 ng/mL and an $AUC_{0\text{-}t}$ of 3170 ng·h/mL on post-natal Day 56). In juvenile females, the NOAEL could not be established based on the delays in sexual maturation that occurred at $\geqslant$ 10 mg/kg. All of the aforementioned effects attributed to the administration of sertraline were reversed at some point during the non-dosing recovery phase of the study. The clinical relevance of these effects observed in rats administered sertraline has not been established.

Animal Studies on Fertility
In two studies conducted in rats, collective evidence did not show an effect on fertility parameters.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sertraline tablets include the following inert ingredients: Calcium hydrogen phosphate, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate, hydroxypropylmethyl cellulose, polyethylene glycol, polysorbates, titanium dioxide (E 171).

6.2 Incompatibilities

None

6.3 Shelf Life

Observe “Expiry Date” (month/year) imprinted on outer pack.

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

Sertraline hydrochloride tablets will be packed in opaque PVC blister packs of 30’s.

7. Product Owner

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