Professional Information for Medicines for Human Use: SERTRALINE AUSTELL

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE

SERTRALINE 50 mg AUSTELL tablets

SERTRALINE 100 mg AUSTELL tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SERTRALINE 50 mg AUSTELL tablet contains sertraline hydrochloride equivalent to 50 mg sertraline.

Each SERTRALINE 100 mg AUSTELL tablet contains sertraline hydrochloride equivalent to 100 mg sertraline.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablets).

SERTRALINE 50 mg AUSTELL tablets:

White to off-white, caplet shaped, biconvex, film-coated tablets with break line on one side and “50” and “BL” embossed on either side of the break line.

SERTRALINE 100 mg AUSTELL tablets:

White to off-white, caplet shaped, biconvex, film-coated tablets with “100” and “BL” embossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SERTRALINE AUSTELL is indicated in adults for the treatment of:

- major depressive disorders such as single episodes and recurrent depression
- obsessive-compulsive disorder (OCD)
- panic disorder, with or without agoraphobia.

SERTRALINE AUSTELL is indicated in children aged 13 – 17 for the treatment of:

- 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 SERTRALINE AUSTELL in long-term use, that is, for more than 12 weeks, has not been systematically evaluated. Therefore, the physician who elects to use SERTRALINE AUSTELL for extended periods should periodically re-evaluate the long-term usefulness of the medicine for the individual patient (see section 4.2).

4.2 Posology and method of administration

Posology

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 also 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 SERTRALINE AUSTELL 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 SERTRALINE AUSTELL, dose changes should not occur at intervals of less than 1 week.

Panic disorder

For panic disorder, the minimum recommended effective dose of SERTRALINE AUSTELL 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

Elderly population

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

Hepatic and renal impairment

See section 4.3 and 4.4.

Discontinuation of treatment

If SERTRALINE AUSTELL therapy has to be discontinued, SERTRALINE AUSTELL should be tapered, (see sections 4.2 and 4.4).

Method of administration

For oral use.

SERTRALINE AUSTELL should be given as a single daily dose with or without food.

4.3 Contraindications

- Hypersensitivity to sertraline or to any of the excipients listed in section 6.1.
- The concomitant use of SERTRALINE AUSTELL 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 under the age of 18 years with both OCD and a major depressive disorder (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) or Neuroleptic Malignant Syndrome (NMS)

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 AUSTELL. The risk of SS or NMS with SSRIs is increased with concomitant use of serotonergic medicines (including amphetamines, triptans and fentanyl and its analogues, and opiate medicines e.g., 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 (MAOIs)

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

Suicide/suicidal thoughts or clinical worsening

All patients treated with SERTRALINE AUSTELL, 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 SERTRALINE AUSTELL, 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 SERTRALINE AUSTELL 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 SERTRALINE AUSTELL, 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, SERTRALINE AUSTELL 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. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8). 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).

Other serotonergic medicines

Co-administration of SERTRALINE AUSTELL with other medicines that enhance the effect of serotonergic neurotransmission, such as amphetamines, tryptophan, fenfluramine 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 SERTRALINE AUSTELL. The majority of reports occurred in patients with

other risk factors for QTc prolongation/TdP. Therefore, SERTRALINE AUSTELL should be used with caution in patients with risk factors for QTc prolongation such as cardiac disease, hypokalaemia or hypomagnesemia, familial history of QTc prolongation, bradycardia and concomitant use of medications which prolong QTc interval (see sections 4.5 and 5.1).

Switching from Selective Serotonin Reuptake Inhibitors (SSRIs), antidepressants or anti-obsessional medicines

There is limited controlled experience regarding the optimal timing of switching from SSRIs, antidepressants or anti-obsessional medicines to sertraline. Care and prudent medical judgment 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

Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants and anti-obsessional medicines, including SERTRALINE AUSTELL. Therefore, SERTRALINE AUSTELL should be used with caution in patients with a history of mania/hypomania. Close surveillance by the medical practitioner is required. Sertraline should be discontinued in any patient entering a manic phase.

Schizophrenia

Psychotic symptoms might become aggravated in schizophrenic patients.

Seizures

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

Sexual dysfunction

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

Hyponatraemia

Hyponatraemia may occur as a result of treatment with SSRIs such as SERTRALINE AUSTELL 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 SERTRALINE AUSTELL. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk. Discontinuation of SERTRALINE AUSTELL 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.

Withdrawal symptoms seen on discontinuation of sertraline treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). It is reported that in clinical trials, among patients treated with sertraline, the incidence of reported withdrawal reactions was 23 % in those discontinuing sertraline compared to 12 % in those who continued to receive sertraline treatment.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sweating, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), confusion, agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions.

Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 – 3 months or more). It is therefore advised that SERTRALINE AUSTELL should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2).

Akathisia/psychomotor restlessness

The use of sertraline has been associated with the development of extrapyramidal symptoms such as akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still and of aggravation of Parkinson's disease (see section 4.8). This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental. Caution should be exercised when prescribing SERTRALINE AUSTELL to patients with extrapyramidal disorders and patients should be carefully monitored.

Bone fractures

Epidemiological studies show an increased risk of bone fractures in patients receiving serotonin reuptake inhibitors (SRIs) including SERTRALINE AUSTELL (see section 4.8). The mechanism leading to this risk is not fully understood.

Concomitant illness

Caution is advisable in using SERTRALINE AUSTELL in patients with diseases or conditions that could affect metabolism or haemodynamic responses.

SERTRALINE AUSTELL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease.

Hepatic impairment

Sertraline is extensively metabolised by the liver.

The elimination half-life of SERTRALINE AUSTELL is prolonged.

The use of SERTRALINE AUSTELL in patients with hepatic disease must be avoided (see section 4.3).

Renal impairment

Sertraline is extensively metabolised, and excretion of unchanged sertraline in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 30 – 60 mL/min) or moderate to severe renal impairment (creatinine clearance < 30 mL/min), multiple-dose pharmacokinetic parameters (AUC_{0-24} or C_{max}) were modest.

SERTRALINE AUSTELL should not be used in patients with renal impairment (see section 4.3).

Use in elderly

It has been reported in clinical studies that the pattern and incidence of adverse reactions in the elderly was similar to that in younger patients.

SSRIs or SNRIs including sertraline have however been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse event (see Hyponatraemia in section 4.4).

Uricosuric effect

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

Diabetes/loss of glycaemic control

Cases of new onset diabetes mellitus have been reported in patients receiving SSRIs including SERTRALINE AUSTELL. 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.

Electroconvulsive therapy

There are no clinical studies establishing the risks or benefits of combined use of ECT and SERTRALINE AUSTELL.

Angle-closure glaucoma

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

Interference with cognitive and motor performance

SERTRALINE AUSTELL does not cause sedation and did not interfere with psychomotor performance.

Weight loss

Significant weight loss may be an undesirable result of treatment with SERTRALINE AUSTELL for some patients, approximately 0,5 – 1,0 kg weight loss.

Grapefruit juice

The administration of SERTRALINE AUSTELL with grapefruit juice is not recommended (see section 4.5).

Interference with urine screening 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.

Laboratory abnormalities

Asymptomatic elevations of serum transaminases (serum glutamic oxaloacetic transaminase (SGOT) also known as aspartate aminotransferase (AST) and serum glutamic pyruvic transaminase (SGPT) also known as alanine aminotransferase (ALT) have been reported infrequently (approximately 0,8 %) in

association with SERTRALINE AUSTELL therapy (see section 4.8). The abnormalities usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

There have been rare reports of altered platelet function and/or abnormal clinical laboratory results in patients taking SERTRALINE AUSTELL.

Paediatric population

SERTRALINE AUSTELL should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with obsessive compulsive disorder aged 13 - 17 years old (see section 4.3).

It has been reported that suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo.

If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for appearance of suicidal symptoms. In addition, only limited clinical evidence is available concerning, long-term safety data in children and adolescents including effects on growth, sexual maturation and cognitive and behavioural developments. A few cases of retarded growth and delayed puberty have been reported post-marketing. The clinical relevance and causality are yet unclear.

Medical practitioners must monitor paediatric patients on long-term treatment for abnormalities in growth and development.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors

Cases of serious reactions, sometimes fatal, have been reported in patients receiving SERTRALINE AUSTELL in combination with a MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. The concomitant use of SERTRALINE AUSTELL with a MAOI is contraindicated (see sections 4.3 and 4.4).

Pimozide

Increased pimozide levels have been demonstrated with SERTRALINE AUSTELL 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 SERTRALINE AUSTELL 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 SERTRALINE AUSTELL (sertraline 200 mg daily) did not potentiate the effects of alcohol, carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects. However, concomitant use of SERTRALINE AUSTELL and alcohol in depressed patients is not recommended.

Lithium

It is recommended that plasma lithium levels be monitored following initiation of SERTRALINE AUSTELL 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 SERTRALINE AUSTELL with medicines such as lithium, which may act via serotonergic mechanisms and patients should be appropriately monitored.

Phenytoin

Increased phenytoin concentrations may occur when SERTRALINE AUSTELL 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 SERTRALINE AUSTELL 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 SERTRALINE AUSTELL.

Triptans

There have been post-marketing reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety, and agitation following the use of SERTRALINE AUSTELL and sumatriptan. Symptoms of serotonergic syndrome may also occur with other products of the same class (triptans). If concomitant treatment with SERTRALINE AUSTELL and triptans is clinically warranted, appropriate observation of the patient is advised (see section 4.4 and Other serotonergic medicines below).

Medicines enhancing serotonergic neurotransmission

Co-administration of SERTRALINE AUSTELL with other medicines which enhance the effect of serotonergic neurotransmission, such other serotonergic medicines e.g., other serotonergic antidepressants, amphetamines, tryptophan and fentanyl, 5-HT antagonists, or the herbal medicine St. John's Wort (*Hypericum perforatum*) with the potential for pharmacodynamic interaction or medicines that impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists with the potential for pharmacokinetic interaction or opioid analgesics, should be undertaken with caution and avoided whenever possible (see section 4.4).

Protein bound medicines

SERTRALINE AUSTELL 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 SERTRALINE AUSTELL 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, SERTRALINE AUSTELL had no significant effects on the protein binding of the substrate (see Warfarin and Other Interactions).

Warfarin

Co-administration of SERTRALINE AUSTELL 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 SERTRALINE AUSTELL therapy is initiated or stopped.

Other interactions - cimetidine, diazepam, tolbutamide, atenolol, glibenclamide and digoxin

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

Co-administration of SERTRALINE AUSTELL with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters.

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

Medicines affecting platelet function

The risk of bleeding may be increased when medicines acting on platelet function (e.g., NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might

increase bleeding risk are concomitantly administered with SSRIs, including sertraline (see section 4.4).

Neuromuscular blockers

SSRIs may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of mivacurium or other neuromuscular blockers.

Electroconvulsive therapy (ECT)

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

Medicines metabolised by cytochrome P450 (CYP) 2D6

There is variability among antidepressants in the extent of clinically important inhibition of the drug metabolising isoenzyme CYP 2D6

In formal interaction studies, chronic dosing with sertraline 50 mg daily showed moderate elevation (mean 23 % - 37 %) of steady state desipramine plasma levels (a marker of CYP 2D6 isoenzyme activity). The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered medicine. Clinical relevant interactions may occur with other CYP 2D6 substrates with a narrow therapeutic index like tricyclic antidepressants (TCAs), typical antipsychotics and class 1C anti-dysrhythmics such as propafenone and flecainide.

Medicines affecting platelet function

The risk of bleeding may be increased when medicines acting on platelet function (e.g., NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might

increase bleeding risk are concomitantly administered with SSRIs, including sertraline (see section 4.4).

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

CYP 3A3/4

Chronic administration of sertraline 200 mg daily does not inhibit the CYP 3A3/4 mediated 6-β hydroxylation of CYP3A4 substrates such as endogenous cortisol or the metabolism of carbamazepine, alprazolam or terfenadine. The results of these studies suggest that sertraline is not a clinically relevant inhibitor of CYP 3A3/4.

It cannot be excluded that other CYP3A4 inducers, e.g., phenobarbital, carbamazepine, St John´s Wort, rifampicin may cause a reduction of sertraline plasma levels.

CYP 2C9

The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of CYP 2C9 substrates tolbutamide, glibenclamide, phenytoin and warfarin suggest that sertraline 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 sertraline 200 mg daily on plasma concentrations of CYP2C19 substrate diazepam suggests that sertraline is not a clinically relevant inhibitor of CYP 2C19.

CYP 1A2

Sertraline has little or no potential to inhibit CYP 1A2.

CYP enzymes inhibitors

Grapefruit juice

Intake of three glasses of grapefruit juice daily reportedly increased the sertraline plasma levels by approximately 100 % in a cross-over study in eight Japanese healthy subjects. Therefore, the intake of grapefruit juice, a CYP3A4 inhibitor, should be avoided during treatment with sertraline (see section 4.4).

CYP3A4 inhibitors

Based on the interaction study with grapefruit juice, it cannot be excluded that the concomitant administration of sertraline and potent CYP3A4 inhibitors, e.g., protease inhibitors, ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin and nefazodone, would result in even larger increases in exposure of sertraline. This also concerns moderate CYP3A4 inhibitors, e.g., aprepitant, erythromycin, fluconazole, verapamil and diltiazem. The intake of potent CYP3A4 inhibitors should be avoided during treatment with sertraline.

CYP2C19 inhibitors

Sertraline plasma levels are enhanced by about 50 % in poor metabolizers of CYP2C19 compared to rapid metabolizers (see section 5.2). Interaction with strong inhibitors of CYP2C19, e.g., omeprazole, lansoprazole, pantoprazole, rabeprazole, fluoxetine, fluvoxamine cannot be excluded.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of child-bearing potential should employ an adequate method of contraception if taking SERTRALINE AUSTELL (see sections 4.3 and 4.4).

Pregnancy

The safety of SERTRALINE AUSTELL during pregnancy and lactation has not been established (see section 4.3).

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage (PPH) following SSRI/SNRI exposure within the month prior to birth (see sections 4.4 and 4.8).

Breastfeeding

Women using SERTRALINE AUSTELL should not breastfeed their infants (see section 4.3).

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

SERTRALINE AUSTELL does not cause sedation and does not interfere with psychomotor performance but may cause hypomania, dizziness, movement disorders, disturbance in attention, visual disturbance, tinnitus and coma. Patients should be cautioned when driving a car or operating machinery until they know SERTRALINE AUSTELL affects them.

4.8 Undesirable effects

a) Summary of the safety profile

Nausea is the most commonly reported undesirable effect. In the treatment of social anxiety disorder, sexual dysfunction (ejaculation failure) reportedly occurred in 14 % men treated with sertraline vs 0 % in placebo. These undesirable effects are dose dependent and are often transient in nature with continued treatment.

The undesirable effects profile commonly reported in double-blind, placebo-controlled studies in patients with OCD, panic disorder, PTSD and social anxiety disorder was similar to that reported in clinical trials in patients with depression.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with sertraline

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations	upper respiratory tract infection, pharyngitis,	gastroenteritis, otitis media, diverticulitis§	

	rhinitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)		neoplasm	
Blood and lymphatic system disorders		lymphadenopathy, thrombocytopenia§, leukopenia§, abnormal platelet function test*	
Immune system disorders		hypersensitivity, seasonal allergy, anaphylactoid reaction	
Endocrine disorders		Hypothyroidism, Hyperprolactinaemia§, inappropriate antidiuretic hormone secretion§	
Metabolism and nutrition disorders	decreased appetite, increased appetite	hypercholesterolaemia, diabetes mellitus, hypoglycaemia, hyperglycaemia§, hyponatraemia§	
Psychiatric disorders	insomnia, anxiety*, depression*,	suicidal ideation/behaviour, psychotic disorder,	

	agitation*, libido decreased*, nervousness, depersonalisation, nightmare, bruxism*	thinking abnormal, apathy, hallucination*, aggression*, euphoric mood*, paranoia, conversion disorder§, paroniria§, drug dependence, sleep walking, premature ejaculation	
Nervous system disorders	dizziness, headache*, somnolence, tremor, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, dystonia, teeth grinding or gait abnormalities), paraesthesia*, hypertonia*, disturbance in attention, dysgeusia	amnesia, hypoaesthesia*, muscle contractions involuntary*, syncope*, hyperkinesia*, migraine*, convulsion*, dizziness postural, coordination abnormal, speech disorder, coma*, akathisia (see section 4.4), dyskinesia, hyperaesthesia,	

		cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome)§, psychomotor restlessness§ (see section 4.4), sensory disturbance, choreoathetosis§, 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§	
Eye disorders	visual disturbance	mydriasis, scotoma, glaucoma,	maculopathy

		diplopia, photophobia, hyphaema§, pupils unequal§, vision abnormal§, lacrimal disorder	
Ear and labyrinth disorders	tinnitus	ear pain	
Cardiac disorders	palpitations	tachycardia, cardiac disorder, myocardial infarction§, Torsade de Pointes (see sections 4.4, 4.5 and 5.1), bradycardia, QTc prolongation (see sections 4.4, 4.5 and 5.1)	
Vascular disorders	hot flush	abnormal bleeding (such as gastrointestinal bleeding) (see section 4.4), hypertension, flushing, haematuria, peripheral ischaemia	
Respiratory, thoracic and	yawning	dyspnoea, epistaxis,	

mediastinal disorders		bronchospasm*, hyperventilation, interstitial lung disease§, laryngospasm, dysphonia, stridor§, hypoventilation, hiccups	
Gastrointestinal disorders	nausea, diarrhoea, dry mouth, dyspepsia, constipation*, abdominal pain*, vomiting*, flatulence	melaena, tooth disorder, oesophagitis, glossitis, haemorrhoids, salivary hypersecretion, dysphagia, eructation, tongue disorder, mouth ulceration, pancreatitis§, haematochezia, tongue ulceration, stomatitis	colitis microscopic*
Hepatobiliary disorders		hepatic function abnormal (see section 4.4), serious liver events (including hepatitis,	

		jaundice and hepatic failure)	
Skin and subcutaneous tissue disorders	hyperhidrosis, rash*	periorbital oedema*, urticaria*, alopecia*, pruritus*, purpura*, dermatitis, dry skin, face oedema, cold sweat, rare reports of severe cutaneous adverse reactions (SCAR): e.g., Stevens-Johnson syndrome and epidermal necrolysis§, skin reaction§, photosensitivity§, angioedema, hair texture abnormal, skin odour abnormal, dermatitis bullous, rash follicular	

Musculoskeletal and connective tissue disorders	back pain, arthralgia, myalgia	osteoarthritis, muscle twitching, muscle cramps, muscular weakness, rhabdomyolysis§, bone disorder	trismus*
Renal and urinary disorders		pollakiuria, micturition disorder, urinary retention, urinary incontinence*, polyuria, nocturia, urinary hesitation*, oliguria	
Reproductive system and breast disorders	ejaculation failure, menstruation irregular, erectile dysfunction	sexual dysfunction (see section 4.4), menorrhagia, vaginal haemorrhage, female sexual dysfunction (see section 4.4), galactorrhoea*, atrophic vulvovaginitis, genital discharge, balanoposthitis§, gynaecomastia, priapism*	postpartum haemorrhage*† (see sections 4.4 and 4.6)

General disorders and administration site conditions	fatigue*, malaise*, chest pain*, asthenia, pyrexia	oedema peripheral*, chills, gait disturbance, thirst, hernia, drug tolerance decreased	
Investigations	weight increased	alanine aminotransferase (ALT) increased*, aspartate aminotransferase (AST) increased*, weight decreased*, blood cholesterol increased, abnormal clinical laboratory results, semen abnormal, altered platelet function[$]	
Injury, poisoning and procedural complications	injury		
Surgical and medical procedures		vasodilation procedure	
* ADR identified post-marketing [§] ADR frequency represented by the estimated upper limit of the 95% confidence interval using "The Rule of 3".			

† This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).

c. Description of selected adverse reactions

Withdrawal symptoms seen on discontinuation of sertraline treatment

Discontinuation of sertraline (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported. Generally these events are mild to moderate and are self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when sertraline treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs (see section 4.4). The mechanism leading to this risk is unknown.

d. Paediatric population

It is reported in over 600 paediatric patients treated with sertraline; the overall profile of adverse reactions was generally similar to that seen in adult studies. The following adverse reactions were reported from controlled trials (n=281 patients treated with sertraline):

Frequent: Headache (22 %), insomnia (21 %), diarrhoea (11 %) and nausea (15 %), chest pain, mania, pyrexia, vomiting, anorexia, affect lability, aggression, agitation, nervousness, disturbance in attention, dizziness, hyperkinesia, migraine, somnolence, tremor, visual disturbance, dry mouth, dyspepsia, nightmare, fatigue, urinary incontinence, rash, acne, epistaxis, flatulence.

Less frequent: ECG QT prolonged (see sections 4.4, 4.5 and 5.1), suicide attempt, convulsion, extrapyramidal disorder, paraesthesia, depression, hallucination, purpura, hyperventilation, anaemia, hepatic function abnormal, alanine aminotransferase increased, cystitis, herpes simplex, otitis externa, ear pain, eye pain, mydriasis, malaise, haematuria, rash pustular, rhinitis, injury, weight decreased, muscle twitching, abnormal dreams, apathy, albuminuria, pollakiuria, polyuria, breast pain, menstrual disorder, alopecia, dermatitis, skin disorder, skin odour abnormal, urticaria, bruxism, flushing.

Frequency unknown: enuresis.

e. Elderly population

SSRIs or SNRIs including sertraline have been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse event (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Toxicity

On the evidence available, SERTRALINE AUSTELL has a wide margin of safety in overdose. Serious sequelae have not been reported following overdoses of SERTRALINE AUSTELL

alone of up to 6 g. Deaths have been reported involving overdoses of sertraline as in SERTRALINE AUSTELL**,** primarily in combination with other medicines and/or alcohol. Therefore, any overdosage should be treated aggressively.

Symptoms

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.

Treatment

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

Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, a cathartic, may be as, or more, effective than emesis or lavage, and should be considered 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 SERTRALINE AUSTELL, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01

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), it is reported that 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

Absorption

After oral administration over the range of 50 to 200 mg once daily for 14 days, mean peak blood levels are reached at 4,5 – 8,4 hours post dose

Distribution

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

Biotransformation

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 the 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.

Elimination

The average terminal plasma half-life is about 26 hours. Steady-state plasma levels are reached after approximately one week of once daily dosing. Consistent with the terminal elimination half-life, there is approximately two-fold accumulation with repeated dosing as compared to a single dose.

Linearity/non-linearity

Sertraline exhibits dose proportional pharmacokinetics over the range 50 mg – 200 mg.

Elderly population

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.

Hepatic impairment

The metabolism of sertraline is delayed in patients with impaired liver function (see sections 4.2, 4.3 and 4.4).

Adolescents

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.

Paediatric population with OCD

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, in order to avoid excessive plasma levels.

Pharmacogenomics

Plasma levels of sertraline were about 50 % higher in poor metabolizers of CYP2C19 versus extensive metabolizers. The clinical meaning is not clear, and patients need to be titrated based on clinical response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Anhydrous calcium hydrogen phosphate

Microcrystalline cellulose

Hydroxypropyl cellulose

Sodium starch glycollate

Magnesium stearate

Tablet film coating

Hydroxypropyl methyl cellulose (Hypromellose)

Polyethylene glycol

Polysorbate 80

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place at or below 25 °C. Protect from light.

Keep blister in outer carton until required for use.

6.5 Nature and contents of container

SERTRALINE 50 mg AUSTELL tablets are packed in white opaque PVC/Aluminium blister packs containing 30 tablets.

SERTRALINE 100 mg AUSTELL tablets are packed in white opaque PVC/Aluminium blister packs containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd

52 Mineral Crescent

Crown Extension 3

Johannesburg, 2090

South Africa

Tel: 0860287835

8. REGISTRATION NUMBERS

SERTRALINE 50 mg AUSTELL tablets: A39/1.2/0286

SERTRALINE 100 mg AUSTELL tablets: A39/1.2/0287

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 April 2006

10. DATE OF REVISION OF THE TEXT

21 June 2022