AUSTRALIAN PRODUCT INFORMATION - NOUMED SERTRALINE (SERTRALINE) 50 MG AND 100 MG TABLETS

1. NAME OF THE MEDICINE

Sertraline hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Noumed Sertraline 50 mg tablets contain 50 mg sertraline (as hydrochloride).

Noumed Sertraline 100 mg tablets contain sertraline 100 mg (as hydrochloride).

Noumed Sertraline tablets also contain inactive ingredients:

Microcrystalline cellulose, calcium hydrogen phosphate, hyprolose, sodium starch glycollate, magnesium stearate, hypromellose, purified talc, titanium dioxide.

3. PHARMACEUTICAL FORM

Noumed Sertraline 50 mg film-coated tablets are white, capsule shaped, scored film-coated tablets, coded SE|50 on one side.

Noumed Sertraline 100 mg film-coated tablets are white, capsule shaped, scored film-coated tablets, coded SE|100 on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of children (aged 6 years and older) and adolescents with obsessive compulsive disorder.

Treatment of major depression, obsessive compulsive disorder and panic disorder in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

Children and adolescents (6 to 18 years)

Obsessive compulsive disorder

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

Adults (18 years and older)

Major depression/Obsessive Compulsive Disorder

Initial treatment. Sertraline treatment should be initiated with a dose of 50 mg once daily. The usual therapeutic dose for depression and OCD is 50 mg/day. While a relationship between dose and antidepressant and antiobsessive effect has not been established, patients were dosed in a range of 50 to 200 mg/day in the clinical trials demonstrating the antidepressive and antiobsessive effectiveness of sertraline. Consequently, patients not responding to a 50 mg/day dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than one week. The onset of therapeutic effect may be seen within seven days; however for full activity two to four weeks are usually necessary for depression, and possibly even longer for OCD.

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

Panic disorder

Initial treatment. Therapy for panic disorder should commence at 25 mg/day, increasing to 50 mg/day after one week. This dosage regimen has been demonstrated to reduce the frequency of early treatment emergent side effects commonly experienced on initiation of treatment of panic disorder. The long term efficacy of sertraline in panic disorder has not been established.

Maintenance, continuation, extended treatment

There is evidence to suggest that depressed patients responding during an initial eight week treatment phase will continue to benefit during an additional 16 weeks of treatment. While there are insufficient data regarding benefits from treatment beyond 24 weeks, it is generally agreed among expert psychopharmacologists that acute episodes of depression require several months or longer of sustained pharmacological therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Discontinuation should be accomplished by a gradual reduction in dosage.

General

The daily dose for all indications may be increased in 50 mg increments over a period of weeks. Dose titrations in 50 mg increments will depend on tolerability and clinical response. The interval between dose increments should be at least one week. The maximum recommended dose of sertraline is 200 mg/day.

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

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

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

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

Use in elderly requires no special precautions. The usual adult dosage is recommended.

4.3 CONTRAINDICATIONS

Known hypersensitivity to sertraline or any of the components in Noumed Sertraline (see Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION).

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

Monoamine oxidase inhibitors. Cases of serious reactions, sometimes fatal, have been reported in patients receiving sertraline in combination with a monoamine oxidase inhibitor (MAOI) including the selective MAOI selegiline and the reversible MAOI (reversible inhibitor of monoamine oxidase (RIMA)) moclobemide, and MAOI drugs, e.g., linezolid (an antibiotic which is a reversible non-selective MAOI) and methylene blue. Some cases presented with features resembling the serotonin syndrome. Similar cases, sometimes fatal, including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma have been reported with other antidepressants during combined treatment with an MAOI and in patients who have recently discontinued an antidepressant or an antiobsessional medicine and have been started on an MAOI. Sertraline should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping sertraline before starting an MAOI.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with caution in the following circumstances

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

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

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 SSRIs, including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of serotonergic drugs (including triptans and fentanyl), with drugs which impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. SS symptoms may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination)

and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Some signs of SS, including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes resemble NMS. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome (see Section 4.3 CONTRAINDICATIONS).

Other serotonergic medicines. Coadministration of SSRIs such as sertraline with other medicines which enhance the effects of serotonergic neurotransmission, such as tryptophan, phentermine, fentanyl and its analogues, tramadol or 5HT agonists, dextromethorphan, tapentadol, pethidine or methadone should be undertaken only with caution and avoided whenever possible due to the potential for pharmacodynamic interaction (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

St John's wort. Concomitant use of the herbal remedy St John's wort (*Hypericum perforatum*) in patients receiving SSRIs should be avoided since there is a possibility of serotonergic potentiation (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Switching from other antidepressants or antiobsessional medicines. There is limited controlled experience regarding the optimal timing of switching from other antidepressants or antiobsessional medicines to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long acting agents. The duration of a washout period for switching from one SSRI to another has not been established.

QTc Prolongation/Torsade de Pointes (TdP). Cases of QTc prolongation and torsade de pointes (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.

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

Weight loss. Significant weight loss may be an undesirable result of treatment with sertraline for some patients but, on average, patients in controlled trials had minimal 0.5 to 1 kg weight loss, versus smaller changes on placebo. Only rarely (< 0.1%) have sertraline patients been discontinued for weight loss. In paediatric patients, weight loss was seen in 2/53 (3.8%) versus 0/54 (0%) of 6 to 12 year old patients and 3/39 (7.7%) versus 0/41 (0%) of 13 to 17 year olds treated with sertraline versus placebo. It is recommended that paediatric patients receiving long-term treatment should be monitored for weight and growth, consistent with good medical care.

Seizures. Seizures are a potential risk with antidepressant and antiobsessional medicines. Seizures were reported in three out of 4,000 patients (0.08%) 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 1,801 patients (0.2%) exposed to sertraline experienced seizures. In the paediatric OCD trial program, the incidence of seizures in the adolescent (13 to 17 year old) population was 3/163 (1.8%) on sertraline compared with 0/41 (0%) on placebo. Seizures/convulsions

were not noted in the 6 to 12 year old patients. In all these cases, the relationship to 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; patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

Clinical worsening and suicide risk associated with psychiatric disorders. The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. The risk must be considered in all depressed patients.

Because of the coexistence of OCD and depression, and panic disorder and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD or panic disorder.

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

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

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

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

to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

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

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

Prescriptions for sertraline should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Weak uricosuric effect. Sertraline is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with sertraline.

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

Hyponatremia. Hyponatremia may occur as a result of treatment with SSRIs (Selective Serotonin Reuptake Inhibitors) or SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors) 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 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 which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

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

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

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

Concomitant illness. Caution is advisable in using Noumed Sertraline in patients with diseases or conditions that could affect metabolism or haemodynamic responses. Sertraline has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received sertraline in double blind trials were evaluated and the data indicate that sertraline is not associated with the development of significant ECG abnormalities.

Use in renal impairment

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

Use in hepatic impairment

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

Use in the elderly

Several hundred elderly patients have participated in clinical studies with sertraline. The pattern of adverse effects 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.

Paediatric use

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

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. Physicians must monitor paediatric patients on long term treatment for abnormalities in growth and development.

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

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

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Monoamine oxidase inhibitors. (see Section 4.3 CONTRAINDICATIONS).

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

Drugs that Prolong the QTc Interval. The risk of QTc prolongation and/or ventricular arrhythmias (e.g. TdP) is increased with concomitant use of other drugs which prolong the QTc interval (e.g. some antipsychotics and antibiotics) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - QTc Prolongation/TdP).

Coadministration of Medicines with Serotonergic Action

Sumatriptan. There have been rare postmarketing 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).

Serotonergic medicines. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

St John's wort. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Potential effects of Coadministration of Medicines Highly Bound to Plasma Proteins. Because sertraline is tightly bound to plasma protein, the administration of sertraline to a patient taking another medicine which is bound to protein may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound sertraline by other protein bound medicines. However, in three formal interaction studies with diazepam, tolbutamide and warfarin respectively, sertraline was

not shown to have any significant effects on the protein binding of the substrate (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, subsections *Warfarin* and *Other Medicine Interactions*).

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

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

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

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

Medicines metabolised by Cytochrome P450 (CYP) 2D6. There is variability among antidepressants in the extent to which they inhibit the activity of isozyme CYP 2D6, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. The clinical significance of this depends on the extent of the inhibition and the therapeutic index of the co-administered medicine. Consequently, concomitant use of a medicine metabolised by CYP 2D6 with sertraline may require lower doses than usually prescribed for the other medicine. Furthermore, whenever sertraline is withdrawn for co-therapy, an increased dose of the co-administered medicine may be required. CYP 2D6 substrates with a narrow therapeutic index include TCAs, class 1C antiarrhythmics such as propafenone and flecainide, and methadone, In formal interaction studies, sertraline 50mg daily produced increases ($p<0.001$) in desipramine C_{max} (44%) and AUC (mean 23-37%).

<u>*Medicines Metabolised by Other CYP Enzymes (CYP 3A3/4, CPY2C9, CYP2C19, CYP1A2)*</u>

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

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

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

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

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

Cimetidine: Coadministration of cimetidine caused a statistically significant increase in sertraline mean AUC by 50% and C_{max}, by 24% and $T_{½}$ by 26%.

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

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

Glibenclamide: No interaction was observed with glibenclamide.

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

Microsomal Enzyme Induction. Preclinical studies have shown sertraline to induce hepatic microsomal enzymes. In clinical studies, sertraline was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days.

Other Interactions

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

Grapefruit juice. The administration of sertraline with grapefruit juice is not recommended.

CNS Depressants and Alcohol. Although sertraline did not potentiate the cognitive and psychomotor effects of alcohol in experiment with normal subjects, the concomitant use of sertraline and alcohol in depressed patients is not recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (giving rise to plasma drug exposure levels similar to or slightly higher than that achieved following the maximum recommended human dose of 200 mg).

Use in pregnancy [Category C]

Medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

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

Teratogenic effects. Reproduction studies have been performed in rats and rabbits at doses up to 80 and 40 mg/kg, respectively, giving rise to plasma drug exposure levels similar to or slightly higher than that achieved following the maximum recommended human dose of 200 mg.

There was no evidence of teratogenicity at any dose level. However, sertraline was associated with delayed ossification in foetuses, probably secondary to effects on the dams.

Nonteratogenic effects. There was also decreased neonatal survival following maternal administration of sertraline at doses giving rise to plasma drug exposure levels similar to or slightly higher than that achieved following the maximum recommended human dose of 200 mg. The decrease in pup survival was shown to be most probably due to in utero exposure to sertraline. The clinical significance of these effects is unknown. Similar effects have been described with other antidepressants.

There are no adequate and well controlled studies in pregnant women. SSRIs have had limited use in pregnancy without a reported increase in birth defects. Because animal reproduction studies are not always predictive of human response, sertraline should not be used during pregnancy unless in the judgment of the doctor, the expected benefit justifies the risk to the foetus. The use of SSRIs in the third trimester may result in a withdrawal state in the newborn infant.

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

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 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 1997-2005 found a PPHN risk ratio of 2.4 (95% CI 1.2-4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy."

Labour and delivery. The effect of sertraline on labour and delivery in humans is unknown.

Use in lactation

Only limited data concerning sertraline levels in breast milk are available. However, in breastfed infants whose mothers were taking sertraline, there have been reports of adverse effects. Because sertraline is excreted in human milk, breastfeeding while on sertraline is not recommended. If sertraline is used during lactation, the physician should be aware that withdrawal reactions have been reported in some neonates whose mothers had been on SSRI antidepressants, including sertraline.

4.7 EFFECT ON ABILITY TO DRIVE OR USE MACHINES

In controlled studies, sertraline did not cause sedation and did not interfere with psychomotor performance. However, as psychotropic drugs may impair the mental or physical attributes required for the performance of potentially hazardous tasks such as driving a car or using machinery the patient should be cautioned accordingly.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Very common:	> 10%
Common:	≥ 1% and < 10%
Uncommon:	≥ 0.1% and < 1%
Rare:	≥ 0.01% and < 0.1%

Placebo-Controlled Clinical Trial Data

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

Autonomic Nervous System. Common: Increase sweating.

Body as a Whole. Very common: Fatigue; *Common*: Hot flushes, fever, malaise, weight decrease, weight increase.

Cardiovascular. Common: Palpitations.

Central and Peripheral Nervous System. Very common: Tremor; *Common*: Convulsions (including myoclonus), hyperkinesia, hypertonia, teeth grinding, hypoaesthesia.

Gastrointestinal. Very common: Nausea; *Common*: Vomiting, dyspepsia.

Psychiatric. Very Common: Insomnia and somnolence; *Common*: Agitation, anxiety, anorexia, concentration impaired, libido decreased, nervousness, paroniria, thinking abnormal, yawning.

Reproductive. Common: Menstrual irregularities, sexual dysfunction (principally ejaculatory delay in males), vaginal haemorrhage.

Skin. Common: Rash, urticaria.

Urinary. Common: Urinary retention.

Vision. Common: Vision abnormal.

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

In a 12 week placebo controlled study in paediatric patients with OCD, adverse events of at least 5% incidence that were seen with a statistically significantly increased level for sertraline compared with placebo were headache, insomnia and agitation in 6 to 12 year olds. For 13 to 17 year olds, the comparable categories were insomnia, anorexia and tremor. Most of the effects seen were mild to moderate in severity. In these clinical trials, sexual dysfunction was

not specifically reported. However, in common with all other SSRIs, sexual dysfunction in males and, to a lesser extent, females has been reported in adult studies.

Clinical Trials in Paediatric MDD Data

In clinical trials in children and adolescents aged 6 to 17 years with major depressive disorder the following adverse events were reported at a frequency of at least 2% of subjects and occurred at a rate of at least twice that of placebo: diarrhoea (9.5% vs 1.6%), agitation (6.3% vs 1.1%), anorexia (5.3% vs 1.1%), vomiting (4.2% vs 1.1%), hyperkinesia (2.6% vs 0.5%), dry mouth (2.1% vs 0.5%), tremor (2.1% vs 0%) and urinary incontinence (2.1% vs 0%). The incidence of discontinuation due to adverse events was 9% (n=17) with sertraline and 2.1% (n=4) with placebo. The most common reasons for discontinuation due to adverse events, whether or not related to sertraline were aggressive reaction (1.6%), agitation (1.63%), suicidal ideation (1.6%), hyperkinesia (1.1%), suicide attempt (1.1%) and aggravated depression (1.1%).

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

Postmarketing Data.

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

Autonomic nervous system. Uncommon: Mydriasis; *Rare*: Priapism.

Body as a whole. Common: Asthenia; *Rare*: allergic reaction, allergy, anaphylactoid reaction, face oedema.

Cardiovascular. Common: Chest pain; *Uncommon*: Hypertension, oedema peripheral, periorbital oedema, syncope, tachycardia; *Rare*: atrial arrhythmia, bradycardia, AV block. *Unknown*: QTc prolongation and torsade de pointes.

Central and Peripheral Nervous System. Common: Movement disorders (such as extrapyramidal symptoms such as akathisia, dystonia and gait abnormalities), paraesthesia; *Uncommon*: migraine; *Rare*: Coma, muscle contractions involuntary. *Unknown*: cerebrovascular spasm (including reversible cerebral vasconstriction syndrome and Call-Fleming syndrome), amnesia. Also reported were signs and symptoms associated with serotonin syndrome: in some cases associated with concomitant use of serotonergic medicines, that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia.

Endocrine. Rare: Galactorrhoea, gynaecomastia, hyperprolactinaemia, hypothyroidism and syndrome of inappropriate ADH secretion (SIADH).

Gastrointestinal. Common: Constipation; *Uncommon:* Appetite increased; *Rare*: pancreatitis.

Hearing/Vestibular. Common: Tinnitus

Haematopoietic. Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding; *Rare*: Altered platelet function, haematuria. leukopenia, thrombocytopenia, increased coagulation times.

Injury, Poisoning and Procedural Complications: *Unknown*: Bone fracture.

Laboratory changes. Rare: abnormal clinical laboratory results. *Unknown*: Electrocardiogram QT prolonged.

Liver, biliary. *Rare*: Serious liver events (including hepatitis, jaundice and liver failure), asymptomatic elevations in serum transaminases (SGOT and SGPT).

Metabolic/Nutritional. Rare: Hyponatraemia, increased serum cholesterol, diabetes mellitus, hyperglycaemia and hypoglycaemia.

Musculoskeletal. *Uncommon*: Arthralgia, muscle cramps; *Rare*: Vasculitis.

Psychiatric. Uncommon: Depressive symptoms, euphoria, hallucination; *Rare*: Aggressive reaction, psychosis, manic reaction, neuroleptic malignant syndrome.

Respiratory. Rare: Bronchospasm. *Unknown*: Dyspnoea.

Skin. Uncommon: Alopecia, pruritus; *Rare*: Angioedema, photosensitivity skin reaction, rare reports of serious exfoliative skin disorders (e.g. Stevens-Johnson syndrome and epidermal necrolysis).

Urinary. Uncommon: Urinary incontinence; *Rare*: enuresis.

Vision. Uncommon: Eye pain; *Rare*: Visual field defect.

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

Medicine abuse and dependence

In human studies, sertraline has not demonstrated potential for abuse. In a placebo-controlled, double-blind, randomised study of comparative abuse liability of sertraline, alprazolam and *d*-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential, such as euphoria or drug liking. As with any CNS active medicine, doctors should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of sertraline misuse or abuse (e.g. development of tolerance, incrementation of dose, drug seeking behaviour).

Reporting suspected adverse effects

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

4.9 OVERDOSE

Symptoms

On the evidence available, sertraline has a wide margin of safety in overdose. Overdoses in adults of 700 to 1200 mg have not resulted in serious symptoms. Ingestion of 4000 mg resulted in seizures in an adolescent. The largest known ingestion is 13.5 g with recovery reported. Another overdose of 2.5 g of sertraline alone resulted in death. Overdosage of 400 and 500 mg in two children have resulted in serotonin syndrome.

Symptoms of overdose include serotonin-mediated side effects such as electrocardiogram QT prolonged, torsade de pointes, somnolence, gastrointestinal disturbances (such as nausea, diarrhoea and vomiting), tachycardia, tremor, agitation and dizziness. Other important adverse events reported with sertraline overdose (single or multiple medicines) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, stupor and syncope. Hyperthermia, increased respirations and cutaneous vasodilation have also been reported. Minor ECG abnormalities, palpitations, prolonged tachycardia and increased pulse rate have also been reported following paediatric overdose. Seizures have been reported rarely. Serotonin syndrome may result following significant overdose, and onset may be delayed. A death due to asthma exacerbation has been reported following sertraline overdose.

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

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

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

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

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Sertraline hydrochloride is an antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents.

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in humans have demonstrated

that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on noradrenaline and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic ($alpha_1$, $alpha_2$, beta), cholinergic, gamma-aminobutyric acid (GABA), dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$) or benzodiazepine receptors; antagonism of such receptors has been hypothesised to be associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic medicines. The chronic administration of sertraline was found in animals to down regulate brain noradrenaline receptors as has been observed with other clinically effective antidepressant and antiobsessional medicines. Sertraline does not inhibit monoamine oxidase.

Medicines known to influence serotonin receptors in animals and isolated cell preparations have been used to investigate possible 5HT receptor abnormalities in patients with OCD. No clear picture has emerged but OCD symptoms were worsened by meta-chlorophenylpiperazine (mCPP), a mixed agonist at serotonin receptors, in untreated OCD patients in comparison to healthy controls, but not after patients had been treated with the nonselective 5HT reuptake inhibitor clomipramine. Tricyclic antidepressants without serotonin reuptake inhibitor (SRI) effects have no efficacy in OCD.

Clinical Trials

Major depression.

Adults. The efficacy of sertraline in the treatment of a major depressive episode in adults was established in controlled trials of six to eight weeks in outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder. Efficacy and safety have been established in studies up to 24 weeks.

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least two weeks). It should include at least four of the following eight symptoms: change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of sertraline in hospitalised depressed patients has not been adequately studied. A study of depressed outpatients who had responded to sertraline during an initial eight week open treatment phase and were then randomised to continuation on sertraline or placebo demonstrated a significantly lower relapse rate over the next eight weeks for patients taking sertraline compared to those on placebo. Therefore, the doctor who elects to use sertraline for extended periods should periodically re-evaluate the long-term usefulness of the medicine for the individual patient.

Obsessive compulsive disorder.

Children and adolescents. The effectiveness of sertraline for the treatment of OCD was first demonstrated in a 12 week, multicentre, parallel group study in a paediatric outpatient population (children and adolescents, ages 6 to 17). Patients in this study were initiated at doses of either 25 mg/day (children, ages 6 to 12) or 50 mg/day (adolescents, ages 13 to 17), and then titrated over the next four weeks to a maximum dose of 200 mg/day, if tolerated. The mean dose for completers was 178 mg/day. Dosing was once a day in the morning or evening. Patients in this study had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS) total score of 22. Patients

receiving sertraline experienced a mean reduction of approximately 7 points on the CYBOCS total score which was significantly greater than the mean 3 point reduction for placebo patients. Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

The safety of sertraline use in children and adolescents, ages 6 to 18, for 52 weeks, was established in a flexible dose, open extension study of 137 patients who had completed the initial 12 week, double blind, placebo controlled study. Sertraline was administered at doses of either 25 mg/day (children, ages 6 to 12) or 50 mg/day (adolescents, ages 13 to 18) and then titrated in weekly 25 mg/day or 50 mg/day increments, respectively, to a maximum dose of 200 mg/day based upon clinical response. The mean dose for completers was 157 mg/day. In this 52 week study sertraline was well tolerated with an adverse event profile generally similar to that observed in the acute 12 week paediatric study. In the 12 week study, a marginally greater number of sertraline treated patients (90%) experienced one or more adverse events (irrespective of causality), when compared to placebo (73%). The majority of adverse events in the sertraline group were classified as mild to moderate in severity.

Adults. The efficacy and safety of sertraline in the treatment of OCD were established in three controlled trials (each 8 to 12 weeks long) of non-depressed adult outpatients with mild, moderate or severe OCD, diagnosed on the basis of DSM-III or DSM-III-R criteria. Efficacy and safety were maintained in a 40 week continuation of the 12 week fixed dose, placebo controlled study. In patients with OCD, the obsessions or compulsions must cause marked distress, be time consuming, or significantly interfere with social or occupational functioning in order to meet the DSM-III-R diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images or impulses that are ego dystonic. Compulsions are repetitive, purposeful and intentional behaviours performed in response to an obsession or in a stereotyped fashion, and are recognised by the person as excessive or unreasonable. In three double blind, multicentre, parallel group, placebo controlled trials, clinically relevant and statistically significant improvements in response rates (40%) were noted in sertraline treatment groups.

In a 12 week double blind fixed dose placebo controlled study in OCD, 26% of patients receiving placebo were regarded as responders to therapy, whereas 40% of patients receiving sertraline were regarded as responders.

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

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

Panic disorder.

Adults. The efficacy and safety of sertraline in the treatment of panic disorder in adults has been evaluated in four double blind, placebo controlled clinical trials for up to 12 weeks: two flexible dose studies and two fixed dose studies. At the last week of treatment (week 10 or 12), both flexible dose studies and one of the fixed dose studies showed statistically significant differences from placebo in favour of sertraline in terms of mean change from baseline in the total number of DSM-III-R defined panic attacks (last observation carried forward analysis).

As the flexible dose studies were of identical protocol, data for these investigations can be pooled. The mean number of full panic attacks at baseline was 6.2/week (n = 167) in the sertraline group and 5.4/week in the placebo group (n = 175). At week 10 (last observation carried forward analysis), the mean changes from baseline were 4.9/week and 2.5/week for the sertraline and placebo groups, respectively. The proportion of patients having no panic attacks at the final evaluation was 69% in the sertraline group and 57% in the placebo group. The mean daily dose administered at the last week of treatment was approximately 120 mg (range: 25 to 200 mg) in the flexible dose studies. All patients entered into clinical trials had a DSM-III-R diagnosis of panic disorder with or without agoraphobia. It was found in the flexible dose studies that initiating treatment at 25 mg/day for one week led to a lower incidence of early discontinuations.

The primary efficacy measure was the number of DSM-III-R defined panic attacks occurring each week. Secondary efficacy variables measured included the Sheehan Panic and Anticipatory Anxiety Scale (PAAS), Hamilton Anxiety (HAM-A) Scale and the Clinical Global Impressions (CGI) rating of severity of Illness and Improvement.

The statistically significant superiority of sertraline over placebo in the treatment of panic disorder was demonstrated by the reduction in the number of panic attacks per week at study endpoint. Analyses of the secondary efficacy variables confirmed that the reduction in panic attack frequency was associated with significant improvement in a broad range of disease symptoms. No clear dose dependency has been demonstrated over the 50 to 200 mg/day dose range investigated in the fixed dose studies. Efficacy beyond 12 weeks has not been assessed.

5.2 PHARMACOKINETIC PROPERTIES

Systemic bioavailability. In humans, following oral once daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 and 8.4 hours after dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once daily dosing. Linear dose proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration-time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately twofold accumulation, compared to a single dose of sertraline, with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a single dose study of sertraline tablets, T_{max} was found to be 2-6 hours and the average half-life was found to be 23 hours (range of 13-37 hours).

The effects of food on the bioavailability of sertraline were studied in subjects administered a single dose with and without food. AUC was slightly increased when the medicine was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration decreased from eight hours after dosing to 5.5 hours. These changes were not considered clinically significant. Animal studies indicate that sertraline has a large apparent volume of distribution.

Metabolism. Sertraline undergoes extensive first-pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than

sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation and glucuronide conjugation. In a study of radiolabelled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40 to 45% of the administered radioactivity was recovered in the urine in nine days. Unchanged sertraline was not detectable in the urine. For the same period, about 40 to 45% of the administered radioactivity was accounted for in faeces, including 12 to 14% unchanged sertraline. Desmethylsertraline exhibits time related, dose dependent increases in AUC_{0-24}, C_{max} and C_{min} with about a five to ninefold increase in these pharmacokinetic parameters between day 1 and day 14.

Protein binding. In vitro protein binding studies performed with radiolabelled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 nanogram/mL. However, at up to 300 and 200 nanogram/mL concentrations respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound medicines, i.e. warfarin and propranolol (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Adults. Sertraline plasma clearance was compared in male and female young subjects (18 to 45 years) and elderly subjects (greater than or equal to 65 years) in an open label, multiple dose study. Eleven subjects in each group received sertraline once daily for 30 days according to a titrated regimen up to 200 mg/day. No significant differences in C_{max}, AUC or elimination half-life were found for the young women or the elderly of either sex. In comparison, C_{max} and AUC were lower and the half-life shorter in young men. Thus, the elimination of sertraline appears to be slightly more rapid in young males. Although these differences are statistically significant, they are unlikely to be clinically significant. The ratios of sertraline clearance to desmethylsertraline clearance of the four groups were similar.

Liver disease. Sertraline is extensively metabolised by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis administered sertraline 50 mg/day for 21 days demonstrated a prolonged elimination half-life and approximately a three-fold greater AUC and C_{max} for sertraline and a two-fold greater AUC and C_{max} for the metabolite in comparison to normal subjects. Patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with hepatic impairment, a lower or less frequent dose should be considered (see such as euphoria or drug liking. As with any CNS active medicine, doctors should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of sertraline misuse or abuse (e.g. development of tolerance, incrementation of dose, drug seeking behaviour).SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Renal disease. In 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) administered sertraline 50 mg/day for 21 days, multiple dose pharmacokinetic parameters AUC_{0-24} or C_{max} were not statistically significantly different compared with controls. This indicates that sertraline dosing does not have to be adjusted based on degree of renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.

Carcinogenicity

The carcinogenic potential of sertraline has not been fully elucidated. Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats (at doses up to 40 mg/kg), giving rise to plasma drug exposure levels similar to or slightly higher than that achieved following the maximum recommended human dose of 200 mg. There was a dose related increase in the incidence of liver adenomas in male mice receiving sertraline at 10 to 40 mg/kg. No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg; this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10 to 40 mg/kg compared to placebo controls, this effect was not clearly medicine related.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

Refer to Section 4.5 – Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF THE CONTAINER

Noumed Sertraline 50 mg film-coated tablets (White, capsule shaped, scored film-coated tablet, coded SE|50 on one side) packed in PVC/Al blister packs of 28 or 30 tablets.

Noumed Sertraline 100 mg film-coated tablets (White, capsule shaped, scored film-coated tablet, coded SE|100 on one side) packed in PVC/Al blister packs of 28 or 30 tablets.

Not all presentations may be marketed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

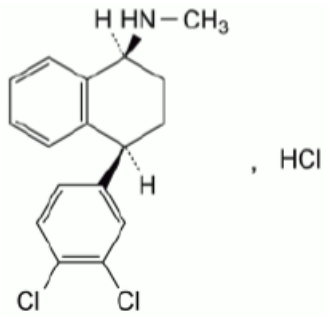
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical Name: (1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine hydrochloride.

Chemical Structure:



Empirical formula: $C_{17}H_{17}NCl_2.HCl$ MW: 342.7

CAS Number: 79559-97-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Avallon Pharmaceuticals Pty Ltd
Level 5, 7 Eden Park Avenue,
Macquarie Park,
North Ryde NSW 2113

Supplied by:
Australian Pharmaceutical Industries
11 Grand Avenue
Camellia, NSW 2142
Australia

9. DATE OF FIRST APPROVAL

28/02/2018

10. DATE OF REVISION

18 November 2019

Summary table of changes

Section changed	Summary of new information
ALL	Reformatted in line with the revised Australian form for providing product information
8	Update sponsor to Blooming Health Pty Ltd.
8	Update sponsor name to Avallon Pharmaceuticals Pty Ltd