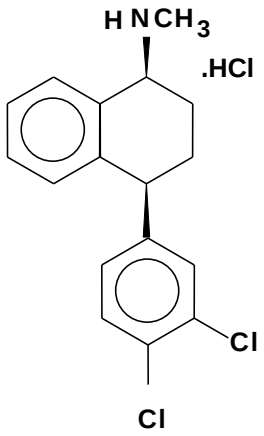
APO-SERTRALINE TABLETS

NAME OF THE MEDICINE

Sertraline hydrochloride.

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

Structural Formula:



Molecular Formula: $C_{17}H_{17}Cl_2N.HCl$

Molecular Weight: 342.7

CAS Registry Number: 79559-97-0

DESCRIPTION

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

Sertraline hydrochloride is a Selective Serotonin Re-uptake Inhibitor (SSRI) antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents.

Sertraline is a disubstituted tetrahydronaphthalene with two asymmetric centres and can exist as four enantiomeric forms in either the trans- or cis- configuration. The cis-(1S,4S) sertraline enantiomer is used.

Each tablet contains sertraline 50 mg or 100 mg (as sertraline hydrochloride).
In addition, each tablet contains the following inactive ingredients: calcium hydrogen phosphate anhydrous, cellulose - microcrystalline, hyprolose, sodium starch glycollate type A, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, polysorbate 80.

PHARMACOLOGY

Pharmacological Actions

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 re-uptake. *In vitro* studies have shown that sertraline has no significant affinity to 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 drugs. The chronic administration of sertraline was found in animals to down regulate brain noradrenaline receptors as has been observed with other clinically effective antidepressant and anti-obsessional drugs. Sertraline does not inhibit monoamine oxidase.
Drugs known to influence serotonin receptors in animals and isolated cell preparations have been used to investigate possible 5HT receptor abnormalities in patients with obsessive-compulsive disorder (OCD). No clear picture has emerged, but OCD symptoms were worsened by meta-chlorophenylpiperazine (mCPP), a mixed agonist at serotonin receptors in untreated OCD patients in comparison to healthy controls, but not after patients had been treated with the non-selective 5HT reuptake inhibitor clomipramine. Tricyclic antidepressants without SRI effects have no efficacy in OCD.

Pharmacokinetics

Absorption

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

The effects of food on the bioavailability of sertraline were studied in subjects administered a single dose with and without food. AUC was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration decreased from 8 hours post-dosing to 5.5 hours. These changes were not considered clinically significant. Animal studies indicate that sertraline has a large apparent volume of distribution.

Distribution

In vitro protein binding studies performed with radiolabelled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see **PRECAUTIONS**).

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. Desmethylsertraline exhibits time-related, dose dependent increases in AUC(0-24 hour), Cmax and Cmin with about a 5–9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Excretion

About 40 to 45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40 to 45% of the administered radioactivity was accounted for in faeces, including 12 to 14% unchanged sertraline.

Adults

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

Hepatic Impairment

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

Renal Impairment

In patients with mild to moderate renal impairment (creatinine clearance 30 mL/min to –60 mL/min) or moderate to severe renal impairment (creatinine clearance 10 mL/min to –29 mL/min) administered sertraline 50 mg/day for 21 days multiple dose pharmacokinetic parameters (AUC0-24 or Cmax) 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.

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 6–8 weeks in outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder. Efficacy and safety have been established in studies up to 24 weeks.

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms; change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of sertraline in hospitalised depressed patients has not been adequately studied. A study of depressed outpatients who had responded to sertraline during an initial 8-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 physician who elects to use sertraline for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Social Phobia (Social Anxiety Disorder)

Adults

The effectiveness of sertraline in the treatment of Social Phobia (Social Anxiety Disorder) was established in two multicentre placebo-controlled studies of adult outpatients who met DSM-IV criteria for Social Phobia (Social Anxiety Disorder). These criteria involve a marked and persistent fear or anxiety of behaving in an embarrassing or humiliating manner while under the gaze of other people in one or more social or performance situations. Exposure to the social or performance situation almost invariably provokes an immediate anxiety response. The patient recognises that the fear is excessive or unreasonable. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the patient's normal routine, occupational (academic) functioning, or social activities, or relationships, or there is marked distress about having the phobia. Performance anxiety, stage fright and shyness in social situations involving unfamiliar people should

not be diagnosed as Social Phobia (Social Anxiety Disorder) unless the anxiety or avoidance leads to clinically significant impairment or marked distress.

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

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

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

Pre-Menstrual Dysphoric Disorder (PMDD)

Adults

The effectiveness of sertraline for the treatment of PMDD was established in two double-blind, parallel group, placebo-controlled flexible dose trials (Studies 1 and 2) conducted over three menstrual cycles. Patients in Study 1 met DSM-III-R criteria for Late Luteal Phase Dysphoric Disorder (LLPDD), the clinical entity now referred to as PMDD in DSM-IV. Patients in Study 2 met DSM-IV criteria for PMDD.

The DSM-IV criteria include markedly depressed mood, anxiety or tension, affective lability and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses. The disturbance markedly interferes with work or school or with usual social activities and relationships by prospective daily ratings during at least two consecutive symptomatic cycles.

Efficacy was assessed with the Daily Record of Severity of Problems (DRSP), a patient-rated instrument that includes assessments for mood, physical symptoms, and other symptoms. Other efficacy assessments included the Hamilton Depression Rating Scale (HAMD-17), and the Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I) scores.

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

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

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

Table 1:

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

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

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

INDICATIONS

Indicated in adults for the treatment of:

- Major depression
- Social phobia (social anxiety disorder) and the prevention of its relapse.
- Pre-menstrual dysphoric disorder (PMDD) as defined by DSM-IV criteria.

CONTRAINDICATIONS

Sertraline is contraindicated in patients with known hypersensitivity to sertraline.

Concomitant use in patients taking pimozide is contraindicated (see **INTERACTIONS WITH OTHER MEDICINES**).

Monoamine Oxidase Inhibitors (MAOI)

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 a MAOI and in patients who have recently discontinued an antidepressant or an anti-obsessional drug and have been started on a MAOI. Sertraline should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping sertraline before starting a MAOI.

PRECAUTIONS

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 **CONTRAINDICATIONS**).

Other Serotonergic Drugs

Co-administration of SSRIs such as sertraline with other drugs that enhance the effects of serotonergic neurotransmission, such as tryptophan, phentermine, fentanyl and its analogues, tramadol or 5-HT agonists, dextromethorphan, tapentadol, pethidine or methadone should be undertaken only with caution and avoided whenever possible due to the potential for pharmacodynamic interaction (see **INTERACTIONS WITH OTHER MEDICINES**).

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 **INTERACTIONS WITH OTHER MEDICINES**).

Switching from Other Antidepressants or Anti-obessional Drugs

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

QTc Prolongation/Torsade de Pointes (TdP)

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

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

Weight Loss

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

Seizures

Seizures are a potential risk with antidepressant and anti-obsessional drugs. Seizures were reported in three out of 4000 patients (0.08%) treated with sertraline in the development programme for depression. No seizures were reported in patients treated with sertraline in the development programme for panic. During the development programme for OCD, four out of 1,801 patients (0.2%) exposed to sertraline experienced seizures. In the paediatric OCD trial programme, the incidence of seizures in the adolescent (13–17 years old) population was 3/163 (1.8%) on sertraline compared with 0/41 (0%) on placebo. Seizures/convulsions were not noted in 6 to 12 year old patients. In all these cases, the relationship 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

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

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

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

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

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

A further pooled analysis of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed the increased risk of suicidal thinking and behaviour (suicidality) during the initial treatment period (generally the first one to two months) extends to young adults (aged 18 to24 years) with major depressive disorder (MDD) and other psychiatric disorders. These studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

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

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

be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for 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.

Abnormal Bleeding/Haemorrhage

Bleeding abnormalities have been reported with the use of SSRIs (including purpura, haematoma, epistaxis, vaginal bleeding , ecchymoses, gastrointestinal bleeding and life threatening haemorrhage). This risk may be potentiated by concurrent use of atypical antipsychotics and phenothiazines, most tricyclic antidepressants non-steroidal anti-inflammatory drugs (NSAIDs), aspirin or other medicines that affect coagulation. 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.

Hyponatraemia

Hyponatraemia 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, hyponatraemia appears to be the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium levels lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatraemia with SSRIs and SNRIs. Also patients taking diuretics or who are otherwise volume-depleted may be at greater risk (see PRECAUTIONS - Use in the Elderly). Discontinuation of sertraline should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatraemia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness 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 Glycaemic 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.

Use in Patients with Concomitant Illness

Caution is advisable in using 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.

Symptoms Associated with Discontinuation

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

Patient should be monitored for these symptoms when discontinuing treatment with sertraline. A gradual reduction in the dose rather than abrupt cessation is recommended wherever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of the treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more graduate rate (see **ADVERSE EFFECTS, PRECAUTIONS - Use in Lactation**; and **DOSAGE AND ADMINISTRATION**).

Drug Abuse And Dependence

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

Electroconvulsive Therapy

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

Use in Pregnancy (Category C)

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

Teratogenic Effects

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

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

Non-Teratogenic 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. animal reproduction studies are not always predictive of human response, sertraline should not be used during pregnancy unless in the judgement of the physician, 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 to 4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2 to 8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy."

Labour and Delivery

The effect of 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 breast-fed infants whose mothers were taking sertraline, there have been reports of adverse effects. Because sertraline is excreted in human milk, breastfeeding while on 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.

Paediatric Use

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

Use in the Elderly

Several hundred elderly patients have participated in clinical studies with sertraline. The pattern of adverse reactions in the elderly was similar to that in younger patients.

Use in Renal Impairment

Sertraline is extensively metabolised. Excretion of unchanged drug in urine is a minor route of elimination. In a study of patients with mild to moderate renal impairment (creatinine clearance 30 mL/min to 60 mL/min) or moderate to severe renal impairment (creatinine clearance 10 mL/min to 29 mL/min) administered sertraline 50 mg/day for 21 days multiple dose pharmacokinetic parameters (AUC_{0-24} or C_{max}) were not statistically significantly different compared 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, 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.

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 200mg.

Genotoxicity

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

Carcinogenicity

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

Effects on Ability to Drive and Use Machine

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.

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.

INTERACTIONS WITH OTHER MEDICINES

Monoamine Oxidase Inhibitors : (see CONTRAINDICATIONS).

Pimozide

Increased pimozide levels have been demonstrated in a study of single low dose pimozide (2 mg) with sertraline co-administration. Co-administration 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 PRECAUTIONS - QTc Prolongation/ Torsade de Pointes).

CNS Depressants & Alcohol

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

Co-administration of Drugs with Serotonergic Action

Sumatriptan

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

Other Serotonergic Drugs: (see **PRECAUTIONS**).

St John's Wort: (see **PRECAUTIONS**).

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

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin re-uptake 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.

Potential Effects of Co-administration of Drugs Highly Bound to Plasma Proteins

Because sertraline is tightly bound to plasma protein, the administration of sertraline to a patient taking another drug which is bound to protein may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound sertraline by other protein bound drugs. However, in three formal interaction studies with diazepam, tolbutamide and warfarin respectively, sertraline was not shown to have any significant effects on the protein binding of the substrate (see sub-sections “Warfarin” and “Other Drug Interactions”).

Warfarin

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

Lithium

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

Phenytoin

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

Drugs Metabolised by Cytochrome P450 CYP2D6

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

Drugs Metabolised by Other CYP Enzymes (CYP3A3/4, CYP 2C9, CYP 2C19, CYP 1A2)

CYP 3A3/4

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

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 sub-sections “Other Drug 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 sub-section “Other Drug Interactions”).

CYP 1A2

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

Other Drug Interactions

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

Cimetidine

Co-administration 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

Co-administration 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 co-administration 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.

ADVERSE EFFECTS

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

Very common:	≥ 10%
Common:	≥ 1% and < 10%
Uncommon:	≥ 0.1% and < 1%
Rare:	≥ 0.01% and < 0.1%
Unknown:	Cannot be estimated from available data

Placebo-Controlled Clinical Trial Data

The following adverse events occurred at a frequency of 1% or more among sertraline patients and at least twice the frequency seen in placebo patients, who participated in placebo-controlled clinical trials (adults – depression, OCD, 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:	Increased 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 mouth, dizziness, diarrhoea/loose stools, headache and abdominal pain (paediatric OCD patients only).

In a 12-week placebo-controlled study in paediatric patients with OCD, adverse events of at least 5% incidence that were seen with a statistically significantly increased level for sertraline compared with placebo were headache, insomnia and agitation in 6–12 year olds. For 13–17 year olds, the comparable categories were insomnia, 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 have been reported in adult studies.

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

Adverse Effects from Clinical Trials in Paediatric MDD

In clinical trials in children and adolescents aged 6 to 17 years with major depressive disorder the following adverse events were reported at a frequency of at least 2% of subjects and occurred at a rate of at least twice that of placebo : diarrhoea (9.5% vs. 1.6%), agitation (6.3% vs. 1.1%), 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 (1.6%), suicidal ideation (1.6%), hyperkinesia (1.1%), suicide attempt (1.1%) and aggravated depression (1.1%).

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

Post-Marketing Experience

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 (including extrapyramidal symptoms such as akathisia, dystonia and gait abnormalities), paraesthesia
Uncommon:	Migraine
Rare:	Coma, muscle contractions involuntary.
Unknown:	Cerebrovascular spasm including reversible cerebral vasoconstriction 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 drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia

Endocrinological

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

Gastrointestinal

Common:	Constipation
Uncommon:	Appetite increased
Rare:	Pancreatitis

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

Hearing / Vestibular:

Common:	Tinnitus

Injury, Poisoning and Procedural Complications

Unknown:	Bone fracture

Investigations and 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:	Angiooedema, 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

DOSAGE AND ADMINISTRATION

Adults (18 Years and Older)

Major Depression

Initial Treatment – Sertraline treatment should be initiated with a dose of 50 mg once daily. The usual therapeutic dose for depression is 50 mg/day. While a relationship between dose and antidepressant effect has not been established, patients were dosed in a range of 50–200 mg/day in the clinical trials demonstrating the antidepressive 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 1 week.

The onset of therapeutic effect may be seen within 7 days; however for full activity 2 to 4 weeks are usually necessary for depression

If no effect is apparent after 6 to 8 weeks, discontinuation of treatment should be considered. Studies of efficacy did not examine the role of psychotherapy.

Social Phobia (Social Anxiety Disorder)

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

Pre-Menstrual Dysphoric Disorder

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

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

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

Maintenance / Continuation / Extended Treatment

There is evidence to suggest that depressed patients responding during an initial 8 week treatment phase will continue to benefit during an additional 16 weeks of treatment. While there are insufficient data regarding benefits from treatment beyond 24 weeks, it is generally agreed among expert psychopharmacologists that acute episodes of depression require several months or longer of sustained pharmacological therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Discontinuation should be accomplished by a gradual reduction in dosage.

General

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

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

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

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

As indicated under **PRECAUTIONS**, particular care should be taken in patients with hepatic impairment.

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

OVERDOSAGE

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

g of sertraline alone resulted in death. Overdosage of 400 and 500 mg in two children have resulted in serotonin syndrome.

Symptoms

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 drugs) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, stupor and syncope. Hyperthermia, increased respirations and cutaneous vasodilation have also been reported. Minor ECG abnormalities, palpitations, prolonged tachycardia and increased pulse rate have also been reported following paediatric overdose. Seizures have been reported rarely. Serotonin syndrome may result following significant overdose, and onset may be delayed. A death due to asthma exacerbation has been reported following sertraline overdose.

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

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

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

Treatment

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

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

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

PRESENTATION AND STORAGE CONDITIONS

APO-Sertraline tablets are intended for oral administration.
Each tablet contains 50 mg or 100 mg of sertraline (as sertraline hydrochloride)

50 mg tablets

White to off white, capsule shaped, biconvex, film coated tablets with breakline on one side and ‘50’ and ‘BL’ embossed on either side of the breakline.
Blister pack PVC/ Aluminium blisters of 30 tablets (AUST R 213177)

100 mg tablets

White to off white, capsule shaped, biconvex, film coated tablets with ‘100’ and ‘BL’ embossed on one side.
Blister pack PVC/ Aluminium blisters of 30 tablets (AUST R 213180).

Not all strengths may be available.

Storage

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
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Macquarie Park NSW 2113

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 27 September 2013

Date of most recent amendment: 26 May 2016