For the Use Only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

SERLIFT TABLETS
(Sertraline Hydrochloride Tablets 50 mg)

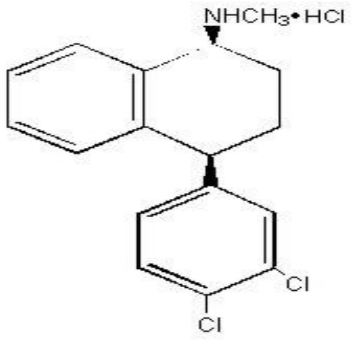
COMPOSITION

Each film coated tablet contains:
Sertraline Hydrochloride
equivalent to Sertraline …… 50 mg
***Excipients*:** Calcium Hydrogen Phosphate, Micrcrystalline Cellulose, Polysorbate-80, Hydroxypropyl Cellulose (Low Viscosity), Purified water, Sodium Starch Glycolate (Type A), Magnesium Stearate. For coating: Opadry OY-52939 Yellow / Opadry OY-50922 Blue, Purified Water.

PRODUCT DESCRIPTION
Blue coloured film coated oval shaped tablets, embossed with 'SLT' on one side and breakline on the other.

DESCRIPTION

SERLIFT TABLETS contain sertraline hydrochloride which is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. Its empirical formula is $C_{17}H_{17}NCl_2$•HCl and it is represented by the following structural formula:



SERTRALINE HYDROCHLORIDE

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamics

Sertraline is a potent and specific inhibitor of neuronal serotonin (5 HT) uptake *in vitro*, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. Sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was reported to be associated with down-regulation of brain norepinephrine receptors as reported with other clinically effective antidepressants and antiobsessional drugs.
Sertraline has not been reported to demonstrate potential for abuse. Sertraline did not produce positive subjective effects indicative of abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforcer in rhesus monkeys trained to self administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

Pharmacokinetics

Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg. In man, following an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of sertraline have been reported to occur at 4.5 to 8.4 hours after the daily administration of the drug. Food does not significantly change the bioavailability of sertraline tablets.

Approximately 98% of the circulating drug is bound to plasma proteins. Sertraline undergoes extensive first-pass hepatic metabolism.

Sertraline is metabolized by multiple pathways including CYP3A4, CYP2C19 and CYP2B6. Sertraline and its major metabolite desmethylsertraline are also substrate of P-glycoprotein *in vitro*.

The mean half-life of sertraline has been reported to be approximately 26 hours (range 22 to 36 hours). Consistent with the terminal elimination half-life, it has been reported that there is an approximately two-fold accumulation up to steady state concentrations, which are achieved after one week of once-daily dosing. The half-life of N-desmethylsertraline has been reported to be in the range of 62 to 104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in faeces and urine in equal amounts. Only a small amount (<0.2%) of unchanged sertraline is excreted in the urine.

Pharmacokinetics in specific patient groups

Adolescents and elderly

The pharmacokinetic profile in adolescents or elderly is not significantly different from that in adults between 18 and 65 years of age.

Liver function impairment
In patients with liver damage, the half-life of sertraline is prolonged and AUC is increased three fold.

Renal impairment
In patients with moderate to severe renal impairment, no significant accumulation of sertraline has been reported.

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

INDICATIONS

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

Sertraline is indicated for the treatment of obsessive-compulsive disorder (OCD). Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of OCD.

Sertraline is indicated for the treatment of panic disorder, with or without agoraphobia. Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of panic disorder.

Sertraline is indicated for the treatment of post-traumatic stress disorder (PTSD). Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of' the initial episode of PTSD.

Sertraline is indicated for the treatment of social phobia (social anxiety disorder). Following satisfaction response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of social phobia.

DOSE AND METHOD OF ADMINISTRATION

SERLIFT TABLET 50 MG may not be suitable for all dosages and therefore, other suitable available strengths and/or dosage forms of sertraline should be used in such cases.

Sertraline should be administered once daily either in the morning or evening.

Sertraline tablets can be administered with or without food.

Initial treatment

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

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

Titration

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

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

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

Use in Children- The safety and effectiveness of sertraline in children have not been fully established. It has been reported that in patients aged 6-17 with depression or OCD, sertraline appeared to have a similar pharmacokinetic profile to that found in adults.

Use in the elderly- The same dose range as in younger patients may be used in the elderly. The pattern and incidence of adverse reactions in the elderly (>65 years of age) has been reported to be similar to that in younger patients.

Use in hepatic insufficiency- The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic Impairment (see **WARNINGS AND PRECAUTIONS**).

Use in renal insufficiency- Sertraline is extensively metabolized. Excretion of unchanged drug in urine is a minor route of elimination. As expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

- Hypersensitivity to the active substance or any of the excipients of the product.
- Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor

and hyperthermia. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see **DRUG INTERACTIONS**).

- Concomitant intake of pimozide is contraindicated (see **DRUG INTERACTIONS**).

WARNINGS AND 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 serotonin syndrome or neuroleptic malignant syndrome with SSRIs is increased with concomitant use of serotonergic drugs (including other serotonergic antidepressants, triptans), with drugs which impair metabolism of serotonin (including MAOIs e.g. methylene blue), antipsychotics and other dopamine antagonists and with opiate drugs. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome (see **CONTRAINDICATIONS**).

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

There is limited controlled experience regarding the optimal timing of switching from SSRIs, antidepressants or anti-obsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents such as fluoxetine.

Other serotonergic drugs e.g. tryptophan, fenfluramine and 5-HT agonists

Co-administration of sertraline with other drugs which enhance the effects of serotonergic neurotransmission such as tryptophan or fenfluramine or 5-HT agonists, or the herbal medicine, St John's Wort (*Hypericum perforatum*), should be undertaken with caution and avoided whenever possible due to the potential for a pharmacodynamic interaction.

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 hypomania or mania

Manic/hypomanic symptoms have been reported to emerge in a small proportion of patients treated with marketed antidepressant and anti-obsessional drugs, including sertraline. Therefore sertraline should be used with caution in patients with a history of mania/hypomania. Close surveillance by the physician is required. Sertraline should be discontinued in any patient entering a manic phase.

Schizophrenia

Psychotic symptoms might become aggravated in schizophrenic patients.

Seizures

Seizures may occur with sertraline therapy: sertraline should be avoided in patients with unstable epilepsy, and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

Suicide / suicidal thoughts / suicide attempts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions, for which sertraline is prescribed, can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of antidepressant drugs in adult patients with psychiatric disorders reported an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Suicidality in Children and Adolescents

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- The indication(s) approved in paediatric for the particular drug should be clearly stated / included.

Paediatric population

Sertraline should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with obsessive compulsive disorder aged 6-17 years old. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently reported among children and adolescents treated with antidepressants. If, based on clinical need, a decision to treat is nevertheless taken; the

patient should be carefully monitored for appearance of suicidal symptoms. In addition only limited reported clinical evidence is available concerning, long-term safety data in children and adolescents including effects on growth, sexual maturation and cognitive and behavioural developments. A few cases of retarded growth and delayed puberty have been reported post-marketing. The clinical relevance and causality are yet unclear. Physicians must monitor paediatric patients on long term treatment for abnormalities in growth and development.

Abnormal bleeding / haemorrhage

There have been reports of cutaneous bleeding abnormalities with SSRIs including cutaneous bleeding (ecchymoses and purpura) and other haemorrhagic events such as gastrointestinal or gynaecological bleeding, including fatal haemorrhages. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function [e.g. anticoagulants, atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs)] as well as in patients with a history of bleeding disorders (see **DRUG INTERACTIONS**).

Hyponatraemia

Hyponatraemia may occur as a result of treatment with SSRIs or SNRIs 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. 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.

Withdrawal symptoms seen on discontinuation of sertraline treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. Among patients treated with sertraline, the incidence of reported withdrawal reactions was 23% in those discontinuing sertraline compared to 12% in those who continued to receive sertraline treatment.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia such as electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, dysphoric mood, irritability, confusion, lethargy, emotional lability, hypomania, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 to 3 months or more). It is therefore advised that sertraline

should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

Akathisia / psychomotor restlessness

The use of sertraline has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hepatic impairment

Sertraline is extensively metabolised by the liver. In subjects with mild, stable cirrhosis, a prolonged elimination half-life and approximately three-fold greater AUC and C_{max} has been reported with multiple dose administration in comparison to normal subjects. No significant differences in plasma protein binding has been reported between the two groups. The use of sertraline in patients with hepatic disease must be approached with caution. If sertraline is administered to patients with hepatic impairment, a lower or less frequent dose should be considered. Sertraline should not be used in patients with severe hepatic impairment.

Renal impairment

Sertraline is extensively metabolised, and excretion of unchanged drug in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 30 to 60 ml/min) or moderate to severe renal impairment (creatinine clearance 10 to 29 ml/min), multiple-dose pharmacokinetic parameters (AUC_{0-24} or C_{max}) have not been reported to be significantly different. Sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Use in elderly

The pattern and incidence of adverse reactions in the elderly has been reported to be similar to that in younger patients.

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

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Electroconvulsive therapy

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

Grapefruit juice

The administration of sertraline with grapefruit juice is not recommended.

Interference with urine screening tests

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

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.

Effects on ability to drive and use machines

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

USE IN SPECIAL POPULATIONS

Pregnancy

There are no reported well controlled studies in pregnant women. However, a substantial amount of reported data did not reveal evidence of induction of congenital malformations by sertraline. An evidence for effects on reproduction probably due to maternal toxicity caused by the pharmacodynamic action of the compound and/or direct pharmacodynamic action of the compound on the foetus has been reported in animals.

Use of sertraline during pregnancy has been reported to cause symptoms, compatible with withdrawal reactions, in some neonates, whose mothers had been on sertraline. This phenomenon has also been reported with other SSRI antidepressants. Sertraline is not recommended in pregnancy, unless the clinical condition of the woman is such that the benefit of the treatment is expected to outweigh the potential risk.

Neonates exposed to sertraline and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Neonates should be observed if maternal use of sertraline continues into the later stages of pregnancy, particularly the third trimester. The following clinical findings / symptoms have been reported or may occur in the neonate after maternal sertraline use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature, instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty in sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome. In a majority of instances, the complications begin immediately or soon (<24 hours) after delivery.

Reported epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The reported risk was approximately 5 cases per 1000 pregnancies. In the general population, 1 to 2 cases of PPHN per 1000 pregnancies occur.

Women of child bearing potential should employ an adequate method of contraception if taking sertraline.
Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

Labor and Delivery: The effect of sertraline on labor and delivery in humans is unknown.

Lactation
Published data concerning sertraline levels in breast milk show that small quantities of sertraline and its metabolite N-desmethylsertraline are excreted in milk. Generally negligible to undetectable levels were found in infant serum, with one exception of an infant with serum levels about 50% of the maternal level (but without a noticeable health effect in this infant). To date, no adverse effects on the health of infants nursed by mothers using sertraline have been reported, but a risk cannot be excluded. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefit outweighs the risk.

Fertility
No adverse effects of sertraline on fertility parameters have been reported in animals. Human case reports with some SSRI's have reported that an effect on sperm quality is reversible. Impact on human fertility has not been reported so far.

DRUG INTERACTIONS

Contraindicated drugs
Monoamine oxidase inhibitors (MAOIs)

Irreversible MAOIs (e.g. selegiline)
Sertraline must not be used in combination with irreversible MAOIs such as selegiline. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see **CONTRAINDICATIONS**).

Reversible, selective MAO-A inhibitor (moclobemide)
Due to the risk of serotonin syndrome, the combination of sertraline with a reversible and selective MAOI, such as moclobemide, should not be given. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of sertraline treatment. It is recommended that sertraline should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see **CONTRAINDICATIONS**).

Reversible, non-selective MAOI (linezolid)

The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with sertraline (see **CONTRAINDICATIONS**).

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on sertraline, or have recently had sertraline therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

Pimozide

Increased pimozide levels of approximately 35% have been reported with a single low dose pimozide (2 mg) [with a mean increase in pimozide AUC and C_{max} of about 40%]. These increased levels were not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated (see **CONTRAINDICATIONS**).

Co-administration with sertraline is not recommended

CNS depressants and alcohol

The co-administration of sertraline 200 mg daily has not been reported to potentiate the effects of alcohol, carbamazepine, haloperidol, or phenytoin on cognitive and psychomotor performance in healthy subjects; however, the concomitant use of sertraline and alcohol is not recommended.

Other serotonergic drugs / triptans / sumatriptan

See **WARNINGS AND PRECAUTIONS**.

Based on the mechanism of action of SNRIs and SSRIs, including sertraline, and the potential for serotonin syndrome, caution is advised, when SNRIs and SSRIs, including sertraline, are coadministered with other drugs that may affect the serotonergic neutrotransmitter systems, such as triptans or fenfluramine or 5-HT agonists, lithium, tramadol, or St. John's Wort. The concomitant use should be avoided whenever possible.

There have been rare reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. Symptoms of serotonergic syndrome may also occur with other products of the same class (triptans). There have been rare reports of serotonin syndrome with use of an SNRI or an SSRI and a triptan. If concomitant treatment of SNRIs and SSRIs (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) with triptans/ sumatriptan is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of sertraline with other SSRIs, SNRIs or tryptophan is not recommended.

Caution is also advised with fentanyl (used in general anaesthesia or in the treatment of chronic pain), other serotonergic drugs (including other serotonergic antidepressants, triptans), and with other opiate drugs.

Drugs requiring Special precautions

Drugs that Prolong the QT Interval
The risk of QTc prolongation and/or ventricular arrhythmias (e.g. TdP) may be increased with concomitant use of other drugs which prolong the QTc interval (e.g. some antipsychotics and antibiotics) (see **WARNINGS AND PRECAUTIONS**).

Lithium
The co-administration of sertraline with lithium has been reported to not significantly alter lithium pharmacokinetics, but reported to result in an increase in tremor, indicating a possible pharmacodynamic interaction. When co-administering sertraline with lithium, patients should be appropriately monitored with appropriate adjustments to the lithium dose.

Phenytoin
Chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, as some case reports have been reported with high phenytoin exposure in patients using sertraline, it is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant medications. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels. It cannot be excluded that other CYP3A4 inducers, e.g. phenobarbital, carbamazepine, St John's Wort, rifampicin may cause a reduction of sertraline plasma levels.

Valproate
The effect of sertraline on valproate levels has not been evaluated. In the absence of such data, it is recommended that plasma valproate levels be monitored following initiation of sertraline therapy with appropriate adjustments to the valproate dose.

CNS active drugs
The risk of using sertraline in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of sertraline and such drugs is required.

There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder and social anxiety disorder to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Warfarin / drugs affecting platelet function / drugs that interfere with haemostasis (non-selective NSAIDs, aspirin, warfarin, etc.)
Co-administration of sertraline 200 mg daily with warfarin has been reported to result in a small but statistically significant increase in prothrombin time, which may in some rare cases unbalance the INR

value. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin.

There was a mean increase in prothrombin time of 8% relative to baseline for sertraline following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either sertraline (50 to 200 mg/day). The normalization of prothrombin time for the sertraline was reported to be delayed. The clinical significance of this change is unknown. Accordingly, patients and prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Serotonin release by platelets plays an important role in haemostasis. An association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also reported that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. The risk of bleeding may be increased when medicines acting on platelet function (e.g. NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might increase bleeding risk are concomitantly administered with SSRIs, including sertraline.

Other drug interactions, digoxin, atenolol, cimetidine, diazepam, tolbutamide

Co-administration with cimetidine has been reported to cause a substantial decrease in sertraline clearance. Significant increases in sertraline mean AUC (50%), C_{max} (24%) and half-life (26%) have been reported. The clinical significance of these changes is unknown. No effect on the beta-adrenergic blocking ability of atenolol has been reported with sertraline. No interaction of sertraline 200 mg daily was reported with digoxin. Co-administration of sertraline 200 mg daily with diazepam or tolbutamide has been reported to result in small statistically significant changes in some pharmacokinetic parameters. There was a 32% decrease relative to baseline in diazepam clearance and there was a 23% increase in T_{max} for desmethyldiazepam reported with sertraline. The clinical significance of these changes is unknown.

Drugs metabolized by cytochrome P450

Drugs metabolized by cytochrome P450 (CYP) 2D6

Sertraline may act as a mild to moderate inhibitor of CYP 2D6 (debrisoquin hydroxylase) and may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. Chronic dosing with sertraline 50 mg daily reported moderate elevation (mean 23% to 37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isozyme activity). Clinical relevant interactions may occur with other CYP 2D6 substrates with a narrow therapeutic index like class 1C antiarrhythmics such as propafenone and flecainide, TCAs and typical antipsychotics, especially at higher sertraline dose levels. Concomitant use of a drug metabolized by P450 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.

Drugs metabolized by other cytochrome enzymes (CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2)

Sertraline does not act as an inhibitor of CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2 to a clinically significant degree. This has been reported to be confirmed *in vivo* with CYP3A4 substrates [endogenous cortisol, carbamazepine, terfenadine, alprazolam), CYP2C19 substrate diazepam, and CYP2C9 substrates tolbutamide, glibenclamide and phenytoin. It has been reported *in vitro* that sertraline has little or no potential to inhibit CYP 1A2.

Sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and C_{max} were reduced by about 35%).

Increase in the sertraline plasma levels by approximately 100% in Japanese has been reported with the intake of three glasses of grapefruit juice daily. Interaction with other CYP3A4 inhibitors has not been established. Therefore, the intake of grapefruit juice should be avoided during treatment with sertraline.

Concomitant administration of sertraline and potent CYP3A4 inhibitors, e.g. protease inhibitors, ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin and nefazodone, may result in increased exposure of sertraline. Similar concerns with moderate CYP3A4 inhibitors, e.g. aprepitant, erythromycin, fluconazole, verapamil and diltiazem may arise. The intake of potent CYP3A4 inhibitors should be avoided during treatment with sertraline.

Sertraline plasma levels have been reported to be enhanced by about 50% in poor metabolizers of CYP2C19 compared to rapid metabolizers. Interaction with strong inhibitors of CYP2C19, e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole, fluoxetine, fluvoxamine cannot be excluded.

Microsomal enzyme induction
Sertraline induces hepatic microsomal enzymes in animals. Sertraline was reported to induce hepatic enzymes minimally as determined by a small but statistically significant decrease in antipyrine half-life. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

Potential effects of coadministration 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 tightly bound to protein (e.g., warfarin, digitoxin) 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 tightly bound drugs.

Tricyclic antidepressant drugs (TCAs)
The extent to which SSRI–TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with sertraline because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored and the dose of TCA may need to be reduced, if a TCA is co-administered with sertraline.

Hypoglycaemic drugs
Administration of sertraline has been reported to cause a statistically significant decrease in the clearance of tolbutamide following an intravenous administration. Sertraline administration has been reported to not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

Electroconvulsive therapy

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

UNDESIRABLE EFFECTS

Nausea is the most common undesirable effect. In the treatment of social anxiety disorder, sexual dysfunction (ejaculation failure) in men has been reported. These undesirable effects are dose dependent and are often transient in nature with continued treatment.

Below given is the list of adverse events reported with sertraline. Some adverse drug reactions listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Very Common	**Common**	**Uncommon**	**Rare**	**Frequency not Known**
Infections and Infestations				
	Pharyngitis	Upper Respiratory Tract Infection, Rhinitis	Diverticulitis, Gastroenteritis, Otitis Media	
Neoplasms benign, malignant (including cysts and polyps)				
			Neoplasm	
Blood and lymphatic system disorders				
			Lymphadenopathy	Leukopenia, Thrombocytopenia
Immune system disorders				
		Hypersensitivity	Anaphylactoid Reaction	Allergy
Endocrine disorders				
		Hypothyroidism		Hyperprolactinaemia, inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders				
	Decreased Appetite, Increased Appetite		Diabetes mellitus, Hypercholesterolaemia, Hypoglycaemia	Hyponatremia hyperglycaemia
Psychiatric Disorders				
Insomnia	Depression, Depersonalisation, Nightmare, Anxiety, Agitation, Nervousness,	Hallucination, Aggression, Euphoric Mood, Apathy, Thinking Abnormal	Conversion Disorder, Drug Dependence, Psychotic disorder, Paranoia, Suicidal ideation/behaviour*,	Paroniria

	Libido Decreased, Bruxism		Sleep Walking, Premature Ejaculation	
Nervous System Disorders				
Dizziness, Somnolence, Headache*	Paraesthesia, Tremor, Hypertonia, Dysgeusia, Disturbance in Attention,	Convulsion, Muscle Contractions Involuntary, Coordination Abnormal, Hyperkinesia, Amnesia, Hypoaesthesia, Speech Disorder, Dizziness Postural, Syncope, Migraine	Coma, Choreoathetosis, Dyskinesia, Hyperaesthesia, Sensory Disturbance	Movement Disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, dystonia, teeth grinding or gait abnormalities). Also reported were signs and symptoms associated with Serotonin Syndrome or Neuroleptic Malignant Syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia. Akathisia and psychomotor restlessness (see **WARNINGS AND PRECAUTIONS**), Cerebrovascular Spasm (including reversible cerebral vasconstriction syndrome and Call-Fleming syndrome).
Eye Disorders				
	Visual Disturbance	Mydriasis	Glaucoma, Lacrimal Disorder, Scotoma, Diplopia, Photophobia, Hyphaema	Vision Abnormal, Pupils Unequal
Ear and Labyrinth Disorders				
	Tinnitus	Ear Pain		
Cardiac Disorders				

	Palpitations	Tachycardia	Myocardial Infarction, Bradycardia, Cardiac Disorder	QTc prolongation, Torsade de Pointes
Vascular Disorders				
	Hot flush	Hypertension, Flushing	Peripheral Ischaemia, Haematuria	Abnormal Bleeding (such as gastrointestinal bleeding)
Respiratory, Thoracic, and Mediastinal Disorders				
	Yawning	Bronchospasm, Dyspnoea, Epistaxis	Laryngospasm, Hyperventilation, Hypoventilation, Stridor, Dysphonia, Hiccups	Interstitial Lung Disease
Gastrointestinal Disorders				
Diarrhoea, Nausea, Dry Mouth Microscopic colitis/ Colitis microscopic**	Abdominal Pain Vomiting, Constipation Dyspepsia, Flatulence	Oesophagitis, Dysphagia, Haemorrhoids, Salivary Hypersecretion, Tongue Disorder, Eructation	Melaena, Haematochezia, Stomatitis, Tongue ulceration, Tooth Disorder, Glossitis, Mouth Ulceration	Pancreatitis
Hepatobiliary Disorders				
			Hepatic Function Abnormal	Serious liver events (including hepatitis, jaundice and Hepatic failure)
Skin and Subcutaneous Tissue Disorders				
	Rash, Hyperhidrosis	Periorbital Oedema, Face Oedema, Purpura, Alopecia, Cold Sweat, Dry skin, Urticaria, Pruritus	Dermatitis, Dermatitis Bullous, Rash Follicular, Hair Texture Abnormal, Skin Odour Abnormal	Rare reports of severe cutaneous adverse reactions (SCAR): e.g. Stevens-Johnson syndrome and epidermal necrolysis, Angioedema, Photosensitivity, Skin Reaction
Musculoskeletal and Connective Tissue Disorders				
	Arthralgia, Myalgia	Osteoarthritis, Muscular Weakness, Back Pain, Muscle Twitching	Bone Disorder	Muscle Cramps
Renal and Urinary Disorders				

		Nocturia, Urinary Retention, Polyuria, Pollakiuria, Micturition disorder, Urinary Incontinence	Oliguria, Urinary Hesitation	
Reproductive System and Breast Disorders				
Ejaculation Failure	Erectile Dysfunction	Vaginal Haemorrhage, Sexual Dysfunction, Female Sexual Dysfunction, Menstruation irregular	Menorrhagia, Atrophic Vulvovaginitis, Balanoposthitis, Genital Discharge, Priapism, Galactorrhoea	Gynaecomastia
General Disorders and Administration Site Conditions				
Fatigue*	Chest Pain, Malaise	Oedema Peripheral, Chills, Pyrexia, Asthenia, Thirst,	Hernia, Drug Tolerance Decreased, Gait Disturbance	
Investigations				
		Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Weight Decreased, Weight Increased	Semen Abnormal, Blood cholesterol increased	Abnormal Clinical Laboratory Results, Altered Platelet Function
Injury and poisoning				
			Injury	
Surgical and medical procedures				
			Vasodilation Procedure	

** Cases of suicidal ideation and suicidal behaviours have been reported during sertraline therapy or early after treatment discontinuation (see **WARNINGS AND PRECAUTIONS**).*

*** ADR identified post-marketing*

Withdrawal symptoms seen on discontinuation of sertraline treatment

Discontinuation of sertraline (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported. Generally these events are mild to moderate and are self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when sertraline

treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see **DOSE AND METHOD OF ADMINISTRATION and WARNINGS AND PRECAUTIONS**).

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

Paediatric population
The overall profile of adverse reactions reported was generally similar to that seen in adult:
Very common: Headache, insomnia, diarrhoea and nausea.

Common: Chest pain, mania, pyrexia, vomiting, anorexia, decreased appetite, affect lability, aggression, agitation, nervousness, disturbance in attention, dizziness, hyperkinesia, migraine, somnolence, tremor, visual disturbance, dry mouth, dyspepsia, nightmare, fatigue, urinary incontinence, rash, acne, epistaxis, flatulence.

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

Frequency not known: enuresis.

Class effects
Epidemiological data mainly in patients 50 years of age and older, reported an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

OVERDOSE
Toxicity
Sertraline has a margin of safety dependent on patient population and/or concomitant medication. Deaths have been reported involving overdoses of sertraline, alone or in combination with other drugs and/or alcohol. Therefore, any overdosage should be medically treated aggressively.

Symptoms
Symptoms of overdose include serotonin-mediated side effects such as somnolence, gastrointestinal disturbances (e.g. nausea and vomiting), tachycardia, tremor, agitation and dizziness. Coma has been reported although less frequently.

QTc prolongation/*Torsade de Pointes* has been reported following sertraline overdose; therefore, ECG-monitoring is recommended in all ingestions of sertraline overdoses.

Management

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

STORAGE
Store below 30°C, protected from moisture

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

PACKING
Blisters of 10 x 10 tablets

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