For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

SERTA

1. Generic name

Sertraline Tablets I.P.

2. Qualitative and quantitative composition

SERTA 100

Each film coated tablet

contains: Sertraline

Hydrochloride I.P.

Equivalent to Sertraline…… 100 mg

Excipients ……..…… q.s

Colours: Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, and Talc.

SERTA 50

Each film coated tablet contains:

Sertraline Hydrochloride I.P.

Equivalent to Sertraline…… 50 mg

Excipients ……q.s

Colours: Yellow Oxide of Iron USPNF & Titanium Dioxide I.P.

The excipients used are Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Polysorbate 80, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, and Yellow Oxide of Iron.

SERTA 25

Each film coated tablet contains: Sertraline

Hydrochloride I.P. Equivalent to Sertraline…… 25 mg

Excipients …… q.s

Colours: Red Oxide of Iron USPNF & Titanium Dioxide I.P.

The excipients used are Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Polysorbate 80, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, Talc and Red Oxide of Iron.

3. Dosage Form And Strength

Dosage Form: Film Coated

Tablet **Strength**: 25, 50 and 100

mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

For the treatment of Major depressive disorder, obsessive compulsive disorder, panic disorders.

4.2 Posology and Method of Administration

Posology

Dose: As directed by physician

Initial treatment

Depression and

OCD

Sertraline treatment should be started at a dose of 50 mg/day.

Panic Disorder, PTSD, and Social Anxiety Disorder

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, Social Anxiety Disorder and PTSD

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

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

Maintenance

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

Depression

Longer-term treatment may also be appropriate for prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during current episode. Patients with depression should be treated for a sufficient period of time of at least 6 months to ensure they are free from symptoms.

Panic disorder and OCD

Continued treatment in panic disorder and OCD should be evaluated regularly, as relapse prevention has not been shown for these disorders.

Elderly patients

Elderly should be dosed carefully, as elderly may be more at risk for hyponatraemia

Patients with hepatic impairment

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. Sertraline should not be used in cases of severe hepatic impairment as no clinical data are available.

Patients with renal impairment

No dosage adjustment is necessary in patients with renal impairment.

Paediatric population

Children and adolescents with obsessive compulsive disorder

Age 13-17 years*:* Initially 50 mg once daily.

Age 6-12 years: Initially 25 mg once daily. The dosage may be increased to 50 mg once daily after one week.

Subsequent doses may be increased in case of less than desired response in 50 mg increments over a period of some weeks, as needed. The maximum dosage is 200 mg daily. However, the generally lower body weights of children compared to those of adults should be taken into consideration when increasing the dose from 50 mg. Dose changes should not occur at intervals of less than one week.

Efficacy is not shown in paediatric major depressive disorder.

No data is available for children under 6 years of age.

Method of administration

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

Sertraline tablet can be administered with or without food.

Withdrawal symptoms seen on discontinuation of sertraline

Abrupt discontinuation should be avoided. When stopping treatment with sertraline the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

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.

Concomitant intake of pimozide is contraindicated.

4.4 Special warnings and precautions for use

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)

The development of potentially life-threatening syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) has been reported with SSRIs, including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of other serotonergic drugs (including other serotonergic antidepressants, amphetamines, 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 SS or NMS syndrome.

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 amphetamines, 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 placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed 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.

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 observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for appearance of suicidal symptoms. In addition, only limited clinical evidence is available concerning, long-term safety data in children and adolescents including effects on growth, sexual maturation and cognitive and behavioural developments. A few cases of retarded growth and delayed puberty have been reported post-marketing. The clinical relevance and causality are yet unclear. Physicians must monitor paediatric patients on long term treatment for abnormalities in growth and development.

Abnormal bleeding/Haemorrhage

There have been reports of 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.

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 (see Use in 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.

Withdrawal symptoms seen on discontinuation of sertraline treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. In clinical trials, among patients treated with sertraline, the incidence

of reported withdrawal reactions was 23% in those discontinuing sertraline compared to 12% in those who continued to receive sertraline treatment.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, 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 reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that sertraline 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. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and approximately three-fold greater AUC and Cmax 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 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 studies of patients with mild to moderate renal impairment (creatinine clearance 30-60 ml/min) or moderate to severe renal impairment (creatinine clearance 10-29 ml/min), multiple-dose pharmacokinetic parameters (AUC_{0-24} or Cmax) were not significantly different compared with controls. Sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Use in elderly

Over 700 elderly patients (>65 years) have participated in clinical studies. The pattern and incidence of adverse reactions in the elderly was similar to that in younger patients.

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

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 mydriasis effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. Sertraline should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma

4.5 Drugs Interactions

Contraindicated

Monoamine Oxidase Inhibitors

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.

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.

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.

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI (e.g. methylene blue) 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 demonstrated in a study of a single low dose pimozide (2 mg). These increased levels were not associated with any changes in EKG. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated.

Co-administration with sertraline is not recommended

CNS depressants and alcohol

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

Other serotonergic drugs

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

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).

Lithium

In a placebo-controlled trial in normal volunteers, the co-administration of sertraline with lithium did not significantly alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When co-administering sertraline with lithium, patients should be appropriately monitored.

Phenytoin

A placebo-controlled trial in normal volunteers suggests that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, as some case reports have emerged of 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. 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.

Triptans

There have been rare post-marketing 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). If concomitant treatment with sertraline and triptans is clinically warranted, appropriate observation of the patient is advised.

Warfarin

Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time, which may in some rare cases unbalance the INR value.

Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Other drug interactions, digoxin, atenolol, cimetidine

Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction of sertraline 200 mg daily was observed with digoxin.

Drugs affecting platelet function

The risk of bleeding may be increased when medicines acting on platelet function (e.g. NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might increase bleeding risk are concomitantly administered with SSRIs, including sertraline.

Neuromuscular Blockers

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

Drugs Metabolized by Cytochrome P450

Sertraline may act as a mild-moderate inhibitor of CYP 2D6. Chronic dosing with sertraline 50 mg daily showed moderate elevation (mean 23%-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.

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 confirmed by *in-vivo* interaction studies with CYP3A4 substrates (endogenous cortisol, carbamazepine, terfenadine, alprazolam), CYP2C19 substrate diazepam, and CYP2C9 substrates tolbutamide, glibenclamide and phenytoin. *In vitro* studies indicate that sertraline has little or no potential to inhibit CYP 1A2.

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

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

Sertraline plasma levels are 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.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Pregnancy

There are no well controlled studies in pregnant women. However, a substantial amount of data did not reveal evidence of induction of congenital malformations by sertraline. Animal studies showed 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. 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 observed 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 should be observed if maternal use of sertraline continues into the later stages of pregnancy, particularly the third trimester. The following symptoms 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. In a majority of instances, the complications begin immediately or soon (<24 hours) after delivery.

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 observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Breast-feeding

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

Animal data did not show an effect of sertraline on fertility parameters.

Human case reports with some SSRI's have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

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

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

Table 1 displays adverse reactions observed from post-marketing experience (frequency not known) and placebo-controlled clinical trials (comprising a total of 2542 patients on sertraline and 2145 on placebo) in depression, OCD, panic disorder, PTSD and social anxiety disorder.

Some adverse drug reactions listed in Table 1 may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Table 1: Adverse Reactions

Frequency of adverse reactions observed from placebo-controlled clinical trials in depression, OCD, panic disorder, PTSD and social anxiety disorder. Pooled analysis and post-marketing experience.

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency Not Known (Cannot be Estimated From the Available Data)
Infections and infestations		upper respiratory tract infection, pharyngitis, rhinitis	gastroenteritis, otitis media	diverticulitis[§]	

Neoplasms benign, malignant and unspecified (including cysts and polyps)			neoplasm		
Blood and lymphatic system disorders				lymphadenopathy, thrombocytopenia*§, leukopenia*§	
Immune system disorders			hypersensitivity*, seasonal allergy*	anaphylactoid reaction*	
Endocrine disorders			hypothyroidism*	hyperprolactinaemia*§, inappropriate antidiuretic	

				hormone secretion*§	
Metabolism and nutrition disorders		decreased appetite, increased appetite*		hypercholesterolaemia, diabetes mellitus*, hypoglycaemia*, hyperglycaemia*§, hyponatraemia*§	
Psychiatric disorders	insomnia	anxiety*, depression*, agitation*, libido decreased*, nervousness, depersonalisation, nightmare, bruxism*	suicidal ideation/behaviour, psychotic disorder*, thinking abnormal, apathy, hallucination*, aggression*, euphoric mood*, paranoia	conversion disorder*§, paroniria*§, drug dependence, sleep walking, premature ejaculation	
Nervous system disorders	dizziness, headache*, somnolence	tremor, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, dystonia, teeth grinding or gait abnormalities), paraesthesia*, hypertonia*, disturbance in attention, dysgeusia	amnesia, hypoaesthesia*, muscle contractions involuntary*, syncope*, hyperkinesia*, migraine*, convulsion*, dizziness postural, coordination abnormal, speech disorder	coma*, akathisia, dyskinesia, hyperaesthesia, cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome)*§, psychomotor restlessness*§, sensory disturbance, choreoathetosis§, also reported were	

				signs and symptoms associated with serotonin syndrome or neuroleptic malignant syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia[§]	
Eye disorders		visual disturbance[*]	mydriasis[*]	scotoma, glaucoma, diplopia, photophobia, hyphaemia[*§], pupils unequal[*§], vision abnormal[§], lacrimal disorder	
Ear and labyrinth disorders		tinnitus[*]	ear pain		
Cardiac disorders		palpitations[*]	tachycardia, cardiac disorder	myocardial infarction[*§], Torsade de Pointes[*§], bradycardia, QTc	

				prolongation*	
Vascular disorders		hot flush*	abnormal bleeding (such as gastrointestinal bleeding)*, hypertension*, flushing, haematuria*	peripheral ischaemia	
Respiratory, thoracic and mediastinal disorders		yawning*	dyspnoea, epistaxis*, bronchospasm*	hyperventilation, interstitial lung disease*§, laryngospasm, dysphonia, stridor*§, hypoventilation, hiccups	
Gastrointestinal disorders	nausea, diarrhoea, dry mouth	dyspepsia, constipation*, abdominal pain*, vomiting*, flatulence	melaena, tooth disorder, oesophagitis, glossitis, haemorrhoids, salivary hypersecretion, dysphagia, eructation, tongue disorder	mouth ulceration, pancreatitis*§, haematochezia, tongue ulceration, stomatitis	
Hepatobiliary disorders				hepatic function abnormal, serious liver events (including hepatitis, jaundice and hepatic failure)	
Skin and subcutaneous tissue disorders		hyperhidrosis, rash*	periorbital oedema*, urticaria*, alopecia*, pruritus*,	rare reports of severe cutaneous adverse reactions	

			purpura*, dermatitis, dry skin, face oedema, cold sweat	(SCAR): e.g. Stevens-Johnson syndrome* and epidermal necrolysis*§, skin reaction*§, photosensitivity§, angioedema, hair texture abnormal, skin odour abnormal, dermatitis bullous, rash follicular	
Musculoskeletal and connective tissue disorders		back pain, arthralgia*, myalgia	osteoarthritis, muscle twitching, muscle cramps*, muscular weakness	rhabdomyolysis*§, bone disorder	trismus*
Renal and urinary disorders			pollakiuria, micturition disorder, urinary retention, urinary incontinence*, polyuria, nocturia	urinary hesitation*, oliguria	
Reproductive system and breast disorders	ejaculation failure	menstruation irregular*, erectile dysfunction	sexual dysfunction, menorrhagia, vaginal haemorrhage, female sexual dysfunction	Galactorrhoea*, atrophic vulvovaginitis, genital discharge, balanoposthitis*§, gynaecomastia*, priapism*	

General disorders and administration site conditions	fatigue*	malaise*, chest pain*, asthenia*, pyrexia*	oedema peripheral*, chills, gait disturbance*, thirst	hernia, drug tolerance decreased	
Investigations		weight increased*	alanine aminotransferase increased*, aspartate aminotransferase increased*, weight decreased*	blood cholesterol increased*, abnormal clinical laboratory results, semen abnormal, altered platelet function*§	
Injury, poisoning and procedural complications		injury			
Surgical and medical procedures				vasodilation procedure	

* ADR identified post-marketing

§ ADR frequency represented by the estimated upper limit of the 95% confidence interval using "The Rule of 3".

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.

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.

Paediatric population

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

Very common (≥1/10): Headache (22%), insomnia (21%), diarrhoea (11%) and nausea (15%).

Common (≥1/100 to <1/10): Chest pain, mania, pyrexia, vomiting, anorexia, affect lability,

aggression, agitation, nervousness, disturbance in attention, dizziness, hyperkinesia, migraine, somnolence, tremor, visual disturbance, dry mouth, dyspepsia, nightmare, fatigue, urinary incontinence, rash, acne, epistaxis, flatulence.

Uncommon (≥1/1000 to <1/100): 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 studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

4.9 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.

5. PHARMACOLOGICAL PROPERTIS

5.1 Mechanism of Action

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. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of

brain norepinephrine receptors as observed with other clinically effective antidepressants and antiobsessional drugs. Sertraline has not demonstrated potential for abuse.

In a reported placebo-controlled, double-blind randomized study of the comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria and abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforce 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.

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors (SSRI), ATC code: N06 AB06

Clinical efficacy and safety

Major Depressive Disorder

A study was conducted which involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50-200 mg/day. These patients (n=295) were randomized to continuation for 44 weeks on double-blind sertraline 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo. The mean dose for completers was 70 mg/day. The % of responders (defined as those patients that did not relapse) for sertraline and placebo arms were 83.4% and 60.8%, respectively.

Post-traumatic stress disorder (PTSD)

Combined data from the 3 studies of PTSD in the general population found a lower response rate in males compared to females. In the two positive general population trials, the male and female sertraline vs. placebo responder rates were similar (females: 57.2% vs 34.5%; males: 53.9% vs 38.2%). The number of male and female patients in the pooled general population trials was 184 and 430, respectively and hence the results in females are more robust and males were associated with other baseline variables (more substance abuse, longer duration, source of trauma etc.) which are correlated with decreased effect.

Paediatric OCD

The safety and efficacy of sertraline (50-200 mg/day) was examined in the treatment of non-depressed children (6-12 years old) and adolescent (13-17 years old) outpatients with obsessive compulsive disorder (OCD). After a one week single blind placebo lead-in, patients were randomly assigned to twelve weeks of flexible dose treatment with either sertraline or placebo. Children (6-12 years old) were initially started on a 25 mg dose. Patients randomized to sertraline showed significantly greater improvement than those randomised to placebo on the Children's Yale-Brown Obsessive Compulsive Scale CY-BOCS ($p = 0.005$) the NIMH Global Obsessive Compulsive Scale ($p=0.019$), and the CGI Improvement ($p = 0.002$) scales. In addition, a trend toward greater improvement in the sertraline group than the placebo group was also observed on the CGI Severity scale ($p=0.089$). For CY-BOCs the mean baseline and change from baseline scores for the placebo group was 22.25 ± 6.15 and -3.4 ± 0.82, respectively, while for the sertraline group, the mean baseline and change from baseline scores were 23.36 ± 4.56 and -6.8 ± 0.87, respectively. In a post-hoc analysis, responders, defined as patients with a 25% or greater decrease in the CY-BOCs (the primary efficacy measure) from baseline to endpoint, were 53% of sertraline-treated patients compared to 37% of placebo- treated patients ($p=0.03$).

Long term safety and efficacy data are lacking for this paediatric

population. Paediatric population

No data is available for children under 6 years of age.

5.3 Pharmacokinetic Properties

Absorption

In man, following an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of sertraline 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.

Distribution

Approximately 98% of the circulating drug is bound to plasma

proteins. Biotransformation

Sertraline undergoes extensive first-pass hepatic metabolism.

Based on clinical and in-vitro data, it can be concluded that 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.

Elimination

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

Linearity/non-linearity

Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg.

Pharmacokinetics in specific patient groups

Paediatric population with OCD

Pharmacokinetics of sertraline was studied in 29 paediatric patients aged 6-12 years old, and 32 adolescent patients aged 13-17 years old. Patients were gradual up titrated to a 200 mg daily dose within 32 days, either with 25 mg starting dose and increment steps, or with 50 mg starting dose or increments. The 25 mg regimen and the 50 mg regimen were equally tolerated. In steady state for the 200 mg dose, the sertraline plasma levels in the 6-12-year-old group were approximately 35% higher compared to the 13-17-year-old group, and 21% higher compared to adult reference group. There were no significant differences between boys and girls regarding clearance. A low starting dose and titration steps of 25 mg are therefore recommended for children, especially with low bodyweight. Adolescents could be dosed like adults.

Adolescents and elderly

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

Hepatic 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-severe renal impairment, there was no significant accumulation of

sertraline.

Pharmacogenomics

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

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Animal Toxicology or Pharmacology

Preclinical data does not indicate any special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenesis. Reproduction toxicity studies in animals showed no evidence of teratogenicity or adverse effects on male fertility. Observed fetotoxicity was probably related to maternal toxicity. Postnatal pup survival and body weight were decreased only during the first days after birth. Evidence was found that the early postnatal mortality was due to in-utero exposure after day 15 of pregnancy. Postnatal developmental delays found in pups from treated dams were probably due to effects on the dams and therefore not relevant for human risk.

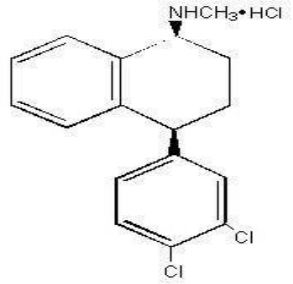
Animal data from rodents and non-rodents does not reveal effects on

fertility. Juvenile animal studies

A juvenile toxicology study in rats has been conducted in which sertraline was administered orally to male and female rats on Postnatal Days 21 through 56 (at doses of 10, 40, or 80 mg/kg/day) with a nondosing recovery phase up to Postnatal Day 196. Delays in sexual maturation occurred in males and females at different dose levels (males at 80 mg/kg and females at ≥10 mg/kg), but despite this finding there were no sertraline-related effects on any of the male or female reproductive endpoints that were assessed. In addition, on Postnatal Days 21 to 56, dehydration, chromorhinorrhea, and reduced average body weight gain was also observed. All of the aforementioned effects attributed to the administration of sertraline were reversed at some point during the nondosing recovery phase of the study. The clinical relevance of these effects observed in rats administered sertraline has not been established.

7. Description

Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride chemical name is (1S, 4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NCl_2 \cdot HCl$ is represented by the following structural formula:



Sertraline Hydrochloride is a white or almost white crystalline powder that is slightly soluble in water, acetone and in 2-propanol and sparingly soluble in ethanol.

SERTA 100

Sertraline Hydrochloride Tablets are shield shaped, biconvex, white, film coated tablets with score on one side. The excipients used are Microcrystalline Cellulose, Sodium Starch

Glycolate, Hydroxy Propyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, and Talc.

SERTA 50

Sertraline Hydrochloride Tablets are oblong shaped, biconvex, yellow, film coated tablets with score on one side. The excipients used are Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Polysorbate 80, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogoland Yellow oxide of Iron.

SERTA 25

Sertraline Hydrochloride Tablets are round, biconvex, peach to pink coloured, film coated tablets with hexagon debossed on one side and score on other side. The excipients used are Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Polysorbate 80, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, Talc and Red Oxide of Iron.

8. PHARMACEUTICAL PARTICULAR

8.1 Incompatibilities

Not available

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

SERTA is available in Blister strips of 15 tablets

8.4 Storage and Handing Instructions

Store at room temperature not exceeding 30°C, protect from light.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the user SERTA 25 mg film coated tablets SERTA 50 mg film coated tablets SERTA 100 mg film coated tablets Sertraline

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What SERTA is and what it is used for

SERTA contains the active substance sertraline. Sertraline is one of a group of medicines called Selective Serotonin Re-Uptake Inhibitors (SSRIs); these medicines are used to treat depression and/or anxiety disorders.

SERTA can be used to treat:

- Depression and prevention of recurrence of depression (in adults).
- Social anxiety disorder (in adults).
- Post-traumatic stress disorder (PTSD) (in adults).
- Panic disorder (in adults).
- Obsessive compulsive disorder (OCD) (in adults and children and adolescents aged 6-17 years old).

Depression is a clinical illness with symptoms like feeling sad, unable to sleep properly or to enjoy life as you used to.

OCD and Panic disorders are illnesses linked to anxiety with symptoms like being constantly troubled by persistent ideas (obsessions) that make you carry out repetitive rituals (compulsions).

PTSD is a condition that can occur after a very emotionally traumatic experience, and has some symptoms that are similar to depression and anxiety. Social anxiety disorder (social phobia) is an illness linked to anxiety. It is characterised by feelings of intense anxiety or distress in social situations (for example: talking to strangers, speaking in front of groups of people, eating or drinking in front of others or worrying that you might behave in an embarrassing manner).

Your doctor has decided that this medicine is suitable for treating your illness.

You should ask your doctor if you are unsure why you have been given SERTA.

9.2 What you need to know before you take SERTA

Do not take SERTA:

- If you are allergic to sertraline or any of the other ingredients of this medicine
- If you are taking or have taken medicines called monoamine oxidase inhibitors (MAOIs such as selegiline, moclobemide) or MAOI like drugs (such as linezolid). If you stop treatment with sertraline, you must wait until at least one week before you start treatment with a MAOI. After stopping treatment with a MAOI, you must wait at least 2 weeks before you can start treatment with sertraline.
- If you are taking another medicine called pimozide (a medicine for mental disorders such as psychosis).

Warnings and precautions

Talk to your doctor or pharmacist before taking SERTA.

Medicines are not always suitable for everyone. Tell your doctor before you take SERTA, if you suffer from or have suffered in the past from any of the following conditions:

- If you have epilepsy (fit) or a history of seizures. If you have a fit (seizure), contact your doctor immediately.
- If you have suffered from manic depressive illness (bipolar disorder) or schizophrenia. If you have a manic episode, contact your doctor immediately.
- If you have or have previously had thoughts of harming or killing yourself (see Below- Thoughts of suicide and worsening of your depression or anxiety disorder).

- If you have Serotonin Syndrome. In rare cases this syndrome may occur when you are taking certain medicines at the same time as sertraline. Your doctor will have told you whether you have suffered from this in the past.

- If you have low sodium level in your blood, since this can occur as a result of treatment with SERTA. You should also tell your doctor if you are taking certain medicines for hypertension, since these medicines may also alter the sodium level in your blood.

- If you are elderly as you may be more at risk of having low sodium level in your blood (see above).

- If you have liver disease; your doctor may decide that you should have a lower dose of SERTA.

- If you have diabetes; your blood glucose levels may be altered due to SERTA and your diabetes medicines may need to be adjusted.

- If you have suffered from bleeding disorders or have been taking medicines which thin the blood (e.g. acetylsalicylic acid (aspirin), or warfarin) or may increase the risk of bleeding.

- If you are a child or adolescent under 18 years old. SERTA should only be used to treat children and adolescents aged 6-17 years old, suffering from obsessive compulsive disorder (OCD). If you are being treated for this disorder, your doctor will want to monitor you closely (see below- Children and adolescents).

- If you are having electro-convulsive therapy (ECT).

- If you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).

- If you have been told that you have an abnormality of your heart tracing after an electrocardiogram (ECG) known as prolonged QT interval.

- If you have heart disease, low potassium levels or low magnesium levels, family history of QT prolongation, low heart rate and concomitant use of medications which prolong QT interval.

Restlessness/Akathisia:

The use of sertraline has been linked to a distressing restlessness and need to move, often being unable to sit or stand still (akathisia). This is most likely to occur during the first few weeks of treatment. Increasing the dose may be harmful so if you develop such symptoms you should talk to your doctor.

Withdrawal reactions:

Side effects relating to stopping treatment (withdrawal reactions) are common, particularly if the treatment is stopped suddenly. The risk of withdrawal symptoms depends on the length of treatment, dosage, and the rate at which the dose is reduced. Generally, such symptoms are mild to moderate. However, they can be serious in some patients. They normally occur within the first few days after stopping treatment. In general, such symptoms disappear on their own and wear off within 2 weeks. In some patients they may last longer (2-3 months or more). When stopping treatment with sertraline it is recommended to reduce the dose gradually over a period of several weeks or months, and you should always discuss the best way of stopping treatment with your doctor.

Thoughts of suicide and worsening of your depression or anxiety disorder:

If you are depressed and/or have anxiety disorders, you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Children and adolescents:

Sertraline should not usually be used in children and adolescents less than 18 years old, except for patients with Obsessive Compulsive Disorder (OCD). Patients under 18 have an increased risk of undesirable effects, such as suicide attempt, thoughts of harming or killing themselves (suicidal thoughts) and hostility (mainly aggressiveness, oppositional behavior and anger) when they are treated with this class of medicines. Nevertheless, it is possible that your doctor decides to prescribe SERTA to a patient under 18 if it is in the patient's interest. If your doctor has prescribed SERTA to you and you are less than 18 years old and you want to discuss this, please contact him/her. Furthermore, if any of the symptoms listed above appear or worsen while you are taking SERTA, you should inform your doctor. Also, the long-term safety of SERTA in regard to growth, maturation and learning (cognitive) and behavioural development in this age group has not yet been demonstrated.

Other medicines and SERTA:

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines can affect the way SERTA works, or SERTA itself can reduce the effectiveness of other medicines taken at the same time.

Taking SERTA together with the following medicines may cause serious side effects:

- Medicines called monoamine oxidase inhibitors (MAOIs), like moclobemide (to treat depression) and selegiline (to treat Parkinson's disease), the antibiotic linezolid and methylene blue (to treat high levels of met haemoglobin in the blood). Do not use SERTA together with these medicines.
- Medicines to treat mental disorders such as psychosis (pimozide). Do not use SERTA together with pimozide.
- Medicines containing amphetamines (used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy, and obesity).
- Herbal medicine containing St. John's Wort (Hypericum perforatum). The effects of St. John's Wort may last for 1-2 weeks.
- Products containing the amino acid tryptophan.
- Medicines to treat severe pain (e.g. tramadol).
- Medicines to treat migraines (e.g. sumatriptan).
- Blood thinning medicine (warfarin).
- Medicines to treat pain/arthritis (Non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen, acetylsalicylic acid (aspirin)).
- Sedatives (diazepam).

- Diuretics (also called 'water' tablets).
- Medicines to treat epilepsy (phenytoin, phenobarbital, carbamazepine).
- Medicines to treat diabetes (tolbutamide).
- Medicines to treat excessive stomach acid, ulcers and heartburn (cimetidine, omeprazole, lansoprazole, pantoprazole, rabeprazole).
- Medicines to treat mania and depression (lithium).
- Other medicines to treat depression (such as amitriptyline, nortriptyline, nefazodone, fluoxetine, fluvoxamine).
- Medicines to treat schizophrenia and other mental disorders (such as perphenazine, levomepromazine and olanzapine).
- Medicines used to treat high blood pressure, chest pain or regulate the rate and rhythm of the heart (such as verapamil, diltiazem, flecainide, propafenone).
- Medicines used to treat bacterial infections (such as rifampicin, clarithromycin, telithromycin, and erythromycin).
- Medicines used to treat fungal infections (such as ketoconazole, itraconazole, posaconazole, voriconazole, fluconazole).
- Medicines used to treat HIV/AIDS and Hepatitis C (protease inhibitors such as ritonavir, telaprevir).
- Medicines used to prevent nausea and vomiting after an operation or chemotherapy (aprepitant).
- Medicines known to increase the risk of changes in the electrical activity of the heart (e.g. some antipsychotics and antibiotics).

SERTA with food, drink and alcohol:

SERTA tablets can be taken with or without food.

Alcohol should be avoided whilst taking SERTA.

Sertraline should not be taken in combination with grapefruit juice, as this may increase the level of sertraline in your body.

Pregnancy, breast-feeding and fertility:

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

The safety of sertraline has not fully been established in pregnant women. Sertraline will only be given to you when pregnant if your doctor considers that the benefit for you is greater than any possible risk to the developing baby.

Make sure your midwife and/or doctor know you are on SERTA. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like SERTA may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby, you should contact your midwife and/or doctor immediately.

Your newborn baby might also have other conditions, which usually begin during the first 24 hours after birth. Symptoms include:

- trouble with breathing,
- A blueish skin or being too hot or cold,

- Blue lips,
- vomiting or not feeding properly,
- being very tired, not able to sleep or crying a lot,
- Stiff or floppy muscles,
- Tremors, jitters or fits,
- increased reflex reactions,
- Irritability,
- Low blood sugar.

If your baby has any of these symptoms when it is born, or you are concerned about your baby's health, contact your doctor or midwife who will be able to advise you.

There is evidence that sertraline passes into human breast milk. Sertraline should only be used in women during breast-feeding, if your doctor considers that the benefit exceeds any possible risk to the baby.

Some medicines like sertraline may reduce the quality of sperm in animal studies. Theoretically, this could affect fertility, but impact on human fertility has not been observed as yet.

Driving and using machines:

Psychotropic drugs such as sertraline may influence your ability to drive or use machines. You should therefore not drive or operate machinery, until you know how this medication affects your ability to perform these activities.

9.3 How to take SERTA

Always take this medicine exactly as your doctor or pharmacist has told you.

Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

Adults:

Depression and Obsessive Compulsive Disorder

For depression and OCD, the usual effective dose is 50 mg/day. The daily dose may be increased in 50 mg increments and at intervals of at least one week over a period of weeks. The maximum recommended dose is 200 mg/day.

Panic disorder, Social anxiety disorder and Post-Traumatic Stress Disorder:

For panic disorder, social anxiety disorder and post-traumatic stress disorder, treatment should be started at 25 mg/day, and increased to 50 mg/day after one week.

The daily dose then may be increased in 50 mg increments over a period of weeks. The maximum recommended dose is 200 mg/day.

Use in children and adolescents:

SERTA must only be used to treat children and adolescents suffering from OCD aged 6-17 years old.

Obsessive Compulsive Disorder:

Children aged 6 to 12: the recommended starting dose is 25 mg daily.

After one week, your doctor may increase this to 50 mg daily. The maximum dose is 200 mg daily.

Adolescents aged 13 to 17: the recommended starting dose is 50 mg daily.

The maximum dose is 200 mg daily.

If you have liver or kidney problems, please tell your doctor and follow the doctor's instructions.

Method of administration:

SERTA tablets may be taken with or without food.

Take your medication once daily either in the morning or evening.

Your doctor will advise you on how long to take this medication for. This will depend on the nature of your illness and how well you are responding to the treatment. It may take several weeks before your symptoms begin to improve. Treatment of depression should usually continue for 6 months after improvement.

If you take more SERTA than you should:

If you accidentally take too much SERTA contact your doctor at once or go to the nearest hospital casualty department. Always take the labelled medicine package with you, whether there is any medication left or not.

Symptoms of overdose may include drowsiness, nausea and vomiting, rapid heart rate, shaking, agitation, dizziness and in rare cases unconsciousness.

If you forget to take SERTA:

Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, do not take the missed dose. Just take the next dose at the right time.

If you stop taking SERTA:

Do not stop taking SERTA unless your doctor tells you to. Your doctor will want to gradually reduce your dose of SERTA over several weeks, before you finally stop taking this medicine. If you suddenly stop taking this medicine you may experience side effects such as dizziness, numbness, sleep disturbances, agitation or anxiety, headaches, feeling sick, being sick and shaking. If you experience any of these side effects, or any other side effects whilst stopping taking SERTA, please speak to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Nausea is the most common side effect. The side effects depend on the dose and often disappear or lessen with continued treatment.

Tell your doctor immediately:

If you experience any of the following symptoms after taking this medicine, these symptoms can be serious.

- If you develop a severe skin rash that causes blistering (erythema multiforme), (this can affect the mouth and tongue). These may be signs of a condition known as Stevens Johnson Syndrome, or Toxic Epidermal Necrolysis (TEN). Your doctor will stop your treatment in these cases.

- Allergic reaction or allergy, which may include symptoms such as an itchy skin rash, breathing problems, wheezing, swollen eyelids, face or lips.

- If you experience agitation, confusion, diarrhoea, high temperature and blood pressure, excessive sweating and rapid heartbeat. These are symptoms of Serotonin Syndrome. In rare cases this syndrome may occur when you are taking certain medicines at

the same time as sertraline. Your doctor may wish to stop your treatment.

- If you develop yellow skin and eyes which may mean liver damage.
- If you experience depressive symptoms with ideas of harming or killing yourself (suicidal thoughts).
- If you start to get feelings of restlessness and are not able to sit or stand still after you start to take SERTA. You should tell your doctor if you start to feel restless.
- If you have a fit (seizure).
- If you have a manic episode.

The following side effects were seen in clinical trials in adults and after marketing.

ery common (may affect more than 1 in 10 people):

Insomnia, dizziness, sleepiness, headache, diarrhoea, feeling sick, dry mouth, ejaculation failure, fatigue.

Common (may affect up to 1 in 10 people):

- Chest cold, sore throat, runny nose,
- decreased appetite, increased appetite,
- Anxiety, depression, agitation, decreased sexual interest, nervousness, feeling strange, nightmare, teeth grinding,
- Shaking, muscular movement problems (such as moving a lot, tense muscles, difficulty walking and stiffness, spasms and involuntary movements of muscles) *, numbness and tingling, muscle tense, lack of attention, abnormal taste,
- Visual disturbance,
- ringing in ears,
- Palpitations,
- Hot flush,
- yawning,
- upset stomach, constipation, abdominal pain, vomiting, gas,
- increased sweating, rash,
- back pain, joint pain, muscle pain,
- Menstrual irregularities, erectile dysfunction,
- Malaise, chest pain, weakness, fever, weight increased, injury.

Uncommon (may affect up to 1 in 100 people):

- gastroenteritis, ear infection,
- tumour,
- hypersensitivity, seasonal allergy,
- low thyroid hormones,
- suicidal thoughts, suicidal behaviour*, psychotic disorder, thinking abnormal, lack of caring, hallucination, aggression, euphoric mood, paranoia,
- amnesia, decreased feeling, involuntary muscle contractions, passing out, moving a lot, migraine, convulsion, dizziness while standing up, abnormal coordination, speech disorder,

- enlarged pupils,
- ear pain,
- fast heartbeat, heart problem
- bleeding problems (such as stomach bleeding) *, high blood pressure, flushing, blood in urine,
- shortness of breath, nose bleed, breathing difficulty, possible wheezing,
- tarry stools, tooth disorder, inflammation of the oesophagus, tongue problem, haemorrhoids, increased saliva, difficulty swallowing, burping, tongue disorder,
- eye swelling, hives, hair loss, itching, purple spots on skin, skin problem with blisters, dry skin, face oedema, cold sweat,
- osteoarthritis, muscle twitching, muscle cramps*, muscular weakness,
- increase in frequency of urination, problem urinating unable to urinate, urinary incontinence, increase in urination, night-time urination,
- sexual dysfunction, excessive vaginal bleeding, vaginal haemorrhage, female sexual dysfunction,
- swelling in legs, chills, difficulty walking, thirst,
- Increase in liver enzyme levels, weight decreased.
- Cases of suicidal ideation and suicidal behaviours have been reported during sertraline therapy or early after treatment discontinuation.

Rare (may affect up to 1 in 1,000 people):

- diverticulitis, swollen lymph glands, decrease in clotting cells*, decrease in white blood cells*,
- severe allergic reaction,
- endocrine problems*,
- high cholesterol, problems controlling blood sugar levels (diabetes), low blood sugar, increase in blood sugar levels*, low blood salt*,
- physical symptoms due to stress or emotions, terrifying abnormal dreams*, drug dependence, sleep walking, premature ejaculation,
- coma, abnormal movements, difficulty moving, increased sensation, sudden severe headache (which may be a sign of a serious condition known as Reversible Cerebral Vasoconstriction Syndrome (RCVS)) *, sensory disturbance,
- spots in front of eyes, glaucoma, double vision, light hurts eye, blood in the eye, unequal sized pupils*, vision abnormal*, tear problem,
- heart attack, light-headedness, fainting, or chest discomfort which could be signs of changes in the electrical activity (seen on electrocardiogram) or abnormal rhythm of the heart*, slow heartbeat,
- poor circulation of arms and legs,
- breathing fast, progressive scarring of lung tissue (Interstitial Lung Disease) *, closing up of throat, difficulty talking, breathing slow, hiccups,
- mouth ulceration, pancreatitis*, blood in stool, tongue ulceration, sore mouth,
- problems with liver function, serious liver function problems*, yellow skin and eyes (jaundice)*,

- skin reaction to sun*, skin oedema*, hair texture abnormal, skin odour abnormal, hair rash,
- breakdown of muscle tissue*, bone disorder,
- urinary hesitation, decreased urination,
- breast discharge, dry vaginal area, genital discharge, red painful penis and foreskin, breast enlargement*, prolonged erection,
- hernia, drug tolerance decreased,
- increase in blood cholesterol levels, abnormal laboratory tests*, semen abnormal, problems with clotting*,
- Relaxation of blood vessels procedure.

Not known: frequency cannot be estimated from the available data:

- lockjaw*,
- bedwetting*.

***Side effect reported after marketing.**

Additional side effects in children and adolescents

In clinical trials with children and adolescents, the side effects were generally similar to adults (see above). The most common side effects in children and adolescents were headache, insomnia, diarrhoea and feeling sick.

Symptoms that can occur when treatment is discontinued

If you suddenly stop taking this medicine you may experience side effects such as dizziness, numbness, sleep disturbances, agitation or anxiety, headaches, feeling sick, being sick and shaking.

An increased risk of bone fractures has been observed in patients taking this type of medicines.

9.5 How to store SERTA

Store at room temperature not exceeding 30°C, protect from light.

9.6 Contents of the pack and other information What SERTA contains

SERTA 100

Each film coated tablet contains as active ingredient

Sertraline Hydrochloride I.P.

Equivalent to Sertraline: 100 mg

Colours: Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, and Talc.

SERTA 50

Each film coated tablet contains as active ingredient

Sertraline Hydrochloride I.P.

Equivalent to Sertraline: 50 mg

Colours: Yellow Oxide of Iron USPNF & Titanium Dioxide I.P.

The excipients used are Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Polysorbate 80, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, and Yellow Oxide of Iron.

SERTA 25

Each film coated tablet contains as active ingredient

Sertraline Hydrochloride I.P.

Equivalent to Sertraline…… 25 mg

Colours: Red Oxide of Iron USPNF & Titanium Dioxide I.P.

The excipients used are Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxy Propyl Cellulose, Polysorbate 80, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, Talc and Red Oxide of Iron.

What SERTA looks like and contents of the pack SERTA 100

Sertraline Hydrochloride Tablets are shield shaped, biconvex, white, film coated tablets with score on one side.

SERTA 50

Sertraline Hydrochloride Tablets are oblong shaped, biconvex, yellow, film coated tablets with score on one side.

SERTA 25

Sertraline Hydrochloride Tablets are round, biconvex, peach to pink coloured, film coated tablets with hexagon debossed on one side and score on other side.

SERTA is available in Blister strips of 15 tablets

10. DETAILS OF MANUFACTURER

Manufactured by:

TORRENT PHARMACEUTICALS LTD.

32 No. Middle Camp, NH-10, East District,

Gangtok, Sikkim – 737 135.

OR

Uni Medicolabs

Plot No. 21 & 22, Phannacity, Selaqui, Dehradun.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Lic No. M/563/2010 issued on 19.12.2019

OR

SERTA 25/100

Mfg. Licence No. 65/UA/2015 issued on 06.01.2021

SERTA 50

Mfg. Licence No. 65/UA/2015 issued on 22.02.2020

12. DATE OF REVISION

Oct 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN /SERTA 25, 50,100 mg/Oct 2022/02/PI