

DATA SHEET

SETRONA

Sertraline 50 mg and 100 mg Tablets (containing sertraline as sertraline hydrochloride)

Presentation

SETRONA 100 mg tablets are white film-coated caplet shaped tablets embossed with '100' on one side and breakline on the other. Each film-coated tablet contains sertraline hydrochloride equivalent to 100 mg sertraline.

SETRONA 50 mg tablets are white film-coated caplet shaped tablets embossed with '50' on one side and breakline on the other. Each film-coated tablet contains sertraline hydrochloride equivalent to 50 mg sertraline.

Uses

Actions

Sertraline is a potent and selective 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 noradrenaline 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 downregulation of brain noradrenaline receptors as observed with other clinically effective antidepressants and antiobsessional drugs.

Sertraline has not demonstrated potential for abuse. In a placebo-controlled, double blind, randomised 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 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.

Clinical Trials

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 randomised 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.

Obsessive-Compulsive Disorder (OCD)

In a long-term study, patients meeting DSM-III-R criteria for OCD who had responded during a 52-week single-blind trial on sertraline 50-200 mg/day (n=224) were randomised to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Patients receiving continued sertraline treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Panic Disorder

In a long-term study, patients meeting DSM-III-R criteria for Panic Disorder who had responded during a 52-week open trial on sertraline 50-200 mg/day (n=183) were randomised to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Patients receiving continued sertraline treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Post-traumatic Stress Disorder (PTSD)

In a long-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on sertraline 50-200 mg/day (n=96) were randomised to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for relapse. Patients receiving continued sertraline treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Social Phobia

In a social phobia relapse prevention study, patients who were responders at the end of a 20 week, multicentre, flexible dose study that compared Sertraline (50-200 mg/day) to placebo, were re-randomised for an additional 24 weeks to either Sertraline continuation treatment (within 50-200 mg/day) or placebo substitution, while placebo responders remained on placebo. Patients receiving Sertraline continuation treatment experienced a statistically significantly lower relapse rate over this 24 week study than patients randomised to placebo substitution treatment.

Pharmacokinetics

Sertraline exhibits dose proportional pharmacokinetics over the range of 50 to 200 mg. In man, following oral once daily dosing over the range of 50 to 200 mg for 14 days, peak plasma concentrations (C_{max}) of sertraline occur at about 4.5 to 8.4 hours post dosing. The pharmacokinetic profile in either adolescents or the elderly is not significantly different from that in adults between 18 and 65 years. The mean half-life of sertraline for young and elderly men and women ranges from 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. Approximately 98% of the circulating drug is bound to plasma

proteins. Animal studies indicate that sertraline has a large apparent volume of distribution. The pharmacokinetics of sertraline in paediatric OCD patients have been shown to be comparable with adults (although paediatric patients metabolise sertraline with slightly greater efficiency). However, lower doses may be advisable for paediatric patients given their lower body weights (especially 6-12 years), in order to avoid excessive plasma levels.

Sertraline undergoes extensive first pass hepatic metabolism. The principal metabolite in plasma, N-desmethylsertraline, is substantially less active (about 20 times) than sertraline *in vitro*, and there is no evidence of activity in *in vivo* models of depression. The half-life of N-desmethylsertraline is in the range of 62-104 hours. Sertraline and N-desmethylsertraline are both extensively metabolised 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.

Food does not significantly change the bioavailability of sertraline tablets.

Indications

Children and Adolescents:

SETRONA is indicated for the treatment of paediatric patients (6- 17 years of age) with OCD.

Adults: SETRONA 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.

SETRONA is indicated for the treatment of obsessive-compulsive disorder (OCD). Following the initial response, sertraline has been associated with sustained efficacy, safety and tolerability for up to 2 years of treatment of OCD.

SETRONA is indicated for the treatment of panic disorder, with or without agoraphobia.

SETRONA is indicated for the treatment of post-traumatic stress disorder (PTSD).

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

SETRONA is indicated for the treatment of premenstrual dysphoric disorder (PMDD).

Dosage and Administration

SETRONA should be administered once daily, either in the morning or evening. SETRONA tablets can be administered with or without food.

Initial Treatment

Use in Children - The safety and efficacy of sertraline has been established in paediatric OCD patients aged 6 to 17. The administration of sertraline to paediatric OCD patients (aged 13 to 17) should commence at 50 mg/day. Therapy for paediatric OCD patients (aged 6 to 12) should commence at 25 mg/day, increasing to 50 mg/day after one week. Subsequent doses may be increased in case of lack of response in 50 mg/day increments, up to 200 mg/day, as needed. In a clinical trial in patients aged 6 to 17 years with depression or OCD, sertraline appeared to have a similar pharmacokinetic profile to that found in adults. However, the generally lower body weights of children compared to those of adults should be taken into consideration in advancing the dose from 50 mg, in order to avoid excessive dosing.

More than 250 paediatric OCD patients have been exposed to sertraline in completed and ongoing studies. The safety profile of sertraline in these paediatric studies is comparable to that observed in adult OCD studies.

The safety and efficacy of sertraline in paediatric patients (under 18 years of age) with depression or panic disorder has not been demonstrated in controlled trials. Consequently, Sertraline Hydrochloride should not be used in patients under 18 years of age (See Warnings).

Adults (18 years and older):

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

Panic Disorder, PTSD and Social Phobia - Therapy for panic disorder, PTSD and social phobia 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.

Premenstrual Dysphoric Disorder – Sertraline treatment should be initiated with a dose of 50 mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment. Patients not responding to a 50 mg/day dose may benefit from dose increases (at 50 mg increments/monthly cycle) up to 150 mg/day when dosing daily throughout the menstrual cycle, or 100 mg/day when dosing during the luteal phase of the menstrual cycle. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilized at the beginning of each luteal phase dosing period.

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

Titration

Children and adolescents (6 up to 18 years):

Titration in Children and Adolescents - Sertraline has an elimination half-life of approximately one day; dose changes should not occur at intervals of less than one week.

Adults (18 years and older):

For all indications other than PMDD - Patients not responding to a 50 mg dose may benefit from dose increases. Dose changes should be made at intervals of at least one week, up to a maximum of 200 mg/day (refer to section above for details on dosage titration for PMDD). The onset of therapeutic effect may be seen within 7 days. However, longer periods are usually necessary to demonstrate therapeutic response, especially in OCD.

Use in the Elderly - The same dose range as in younger patients may be used in the elderly. Over 700 elderly patients (>65 years) have participated in clinical studies which demonstrated the efficacy of sertraline in this patient population. The pattern and incidence of adverse reactions in the elderly was 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 metabolised. 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*).

Maintenance

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

Contraindications

SETRONA is contraindicated in patients with a known hypersensitivity to sertraline. Concomitant use in patients taking pimozide is contraindicated (see *Interactions*). Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see *Warnings and Precautions*).

Warnings and Precautions

The authority to prescribe medicines is controlled by the Medicines Act 1981, however, such prescribing needs to be in conformance with the Code of Health and Disability Services Consumers' Rights 1996. The patient has the right to treatment meeting appropriate ethical and professional standards and the patient needs to be fully

informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

Information for Patients and Families: Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early on during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Monoamine Oxidase Inhibitors: Cases of serious reactions, sometimes fatal, have been reported in patients receiving sertraline in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI, selegiline and the reversible MAOI, moclobemide. Some cases presented with features resembling serotonin syndrome, the symptoms of which include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. Therefore, sertraline should not be used in combination with an MAOI or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should elapse after discontinuing sertraline treatment before starting an MAOI (see *Contraindications*).

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) - The development of potentially life-threatening syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) has been reported with SSRIs, including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of serotonergic drugs (including triptans and fentanyl*), with drugs which impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. SS symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Some signs of SS, including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes resemble NMS. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome (see CONTRAINDICATIONS).

Other Serotonergic Drugs - Coadministration of SSRIs such as sertraline with other drugs which enhance the effects of serotonergic neurotransmission, such as tryptophan, fenfluramine, phentermine, tramadol or 5-HT agonists should be undertaken only with caution and avoided whenever possible due to the potential for pharmacodynamic interaction.

St John's Wort - Concomitant use of the herbal remedy St John's Wort (*Hypericum perforatum*) in patients receiving SSRIs should be avoided since there is a possibility of serotonergic potentiation.

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

antiobsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents such as fluoxetine. The duration of a washout period for switching from one SSRI to another has not been established.

Activation of Mania/Hypomania - During premarketing testing, hypomania or mania occurred in approximately 0.4% of sertraline treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder treated with other marketed antidepressant and antiobsessional drugs.

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

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

Seizures - Seizures are a potential risk with antidepressant and antiobsessional drugs. Seizures were reported in approximately 0.08% of patients treated with sertraline in the development program for depression. No seizures were reported in patients treated with sertraline in the development program for panic. During the development program for OCD, four out of approximately 1,800 patients exposed to sertraline experienced seizures (approximately 0.2%). Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. In all these cases, the relationship to sertraline therapy was uncertain. Since sertraline has not been evaluated in patients with a seizure disorder, it should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

Mania and Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that Sertraline Hydrochloride is not approved for use in treating bipolar depression.

Clinical worsening and Suicide Risk:- Since the possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs, patients should be closely supervised during the early course of therapy.

Because of the well-established comorbidity between OCD and depression, panic disorder and depression, PTSD and depression, social phobia (social anxiety disorder) and depression, and PMDD and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD, panic disorder, PTSD, social phobia or PMDD.

The risk of suicide attempts must be considered especially in depressed patients.

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

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

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

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

was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

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

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

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

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

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

Hyponatremia - Hyponatremia may occur as a result of treatment with SSRIs (Selective Serotonin Reuptake Inhibitors) or SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors) including sertraline. In many cases, hyponatremia appears to be the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium levels lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also patients taking diuretics or who are otherwise volume-depleted may be at greater risk. Discontinuation of sertraline should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness which may lead to falls. Signs and

symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

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

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

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

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.

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

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

Use in Hepatic Disease - 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 C_{max} in comparison to normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.

Use in Renal Disease - Sertraline is extensively metabolised. 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 (AUC₀₋₂₄ or C_{max}) were not significantly different compared with controls. Half-lives were similar and there were no differences in plasma protein binding in all groups studied. This study indicates that, as expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment.

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

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

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

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

Use in Pregnancy and Lactation –Category C. Medicines which, owing to their pharmacological effects have caused or may be suspected of causing, harmful effects

on the human fetus or neonate without causing malformations. These effects may be reversible.

Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 and 10 times the maximum daily human mg/kg dose respectively. There was no evidence of teratogenicity at any dose level. At the dose level corresponding to approximately 2.5 to 10 times the maximum daily human mg/kg dose, however, sertraline was associated with delayed ossification processes in foetuses, probably secondary to effects on the dams.

There was decreased neonatal survival following maternal administration of sertraline at doses of approximately 5 times the maximum human mg/kg dose. Similar effects on neonatal survival have been described for other antidepressant drugs. The clinical significance of these effects is unknown.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sertraline should be used during pregnancy only if the perceived benefits outweigh the risks.

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

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997-2005 found a PPHN risk ratio of 2.4 (95% CI 1.2-4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy". Some epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of SSRIs and SNRIs in pregnancy. The relevance for sertraline treatment remains unknown. Some epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Isolated studies in small numbers of nursing mothers and their infants indicated negligible or undetectable levels of sertraline in infant serum, although levels in breast

milk were more concentrated than in maternal serum. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefit outweighs the risk.

If sertraline is used during pregnancy and/or lactation, the physician should be aware of post-marketing reports of symptoms, including those compatible with withdrawal reactions, in some neonates whose mothers had been on SSRI antidepressants, including sertraline.

Women of childbearing potential should employ an adequate method of contraception if taking sertraline.

Paediatric Use (under 18 years of age) - A total of 225 paediatric patients have completed OCD trials with sertraline. The safety profile of Sertraline in these paediatric studies is comparable to that observed in the adult OCD studies. Safety and effectiveness in paediatric patients below the age of 6 have not been established.

In clinical trials, adverse events related to suicidality (suicidal thoughts and suicidal behaviours) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with SSRIs (and Venlafaxine) compared to those treated with placebo.

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

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

Adverse Effects

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

Very common: $\geq 10\%$

Common: $\geq 1\%$ and $< 10\%$

Uncommon: $\geq 0.1\%$ and $< 1\%$

Rare: $\geq 0.01\%$ and $< 0.1\%$

Placebo-Controlled Clinical Trial Data

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

Autonomic Nervous System:

Common: Increased sweating

Body as a Whole:

Very common: Fatigue;

Common: Hot flushes, fever, malaise, weight decrease, weight increase

Cardiovascular:

Common: Palpitations

Central and Peripheral Nervous System:

Very common: Tremor;

Common: Convulsions (including myoclonus), hyperkinesia, hypertonia, teeth grinding, hypoaesthesia

Gastrointestinal:

Very common: Nausea;

Common: Vomiting, dyspepsia

Psychiatric:

Very common: Insomnia and somnolence;

Common: Agitation, anxiety, anorexia, concentration impaired, libido decreased, nervousness, paroniria, thinking abnormal, yawning.

Reproductive:

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

Skin:

Common: Rash, urticaria

Urinary:

Common: Urinary retention

Eye Disorders

Common: Mydriasis and vision abnormal

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

In a 12-week placebo-controlled study in paediatric patients with OCD, adverse events of at least 5% incidence that were seen with a statistically significantly increased level for sertraline compared with placebo were headache, insomnia and agitation in 6-12 year olds. For 13-17 year olds, the comparable categories were insomnia, anorexia and tremor. Most of the effects seen were mild to moderate in severity. In these clinical trials, sexual dysfunction was not specifically reported. However, in common with all other SSRIs, sexual dysfunction in males and, to a lesser extent, females have been reported in adult studies.

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

No weight gain was observed in controlled clinical trials with sertraline treatment for depression or OCD; some patients may experience a reduction in body weight with sertraline.

Adverse Reactions from Clinical Trials in Paediatric MDD

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

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

Post-Marketing Data

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

Autonomic Nervous System:

Uncommon: Mydriasis;

Rare: Priapism

Body as a Whole:

Common: Asthenia;

Rare: Allergic reaction, allergy, anaphylactoid reaction

Cardiovascular:

Common: Chest pain;

Uncommon: Hypertension, oedema peripheral, periorbital oedema, syncope, tachycardia;

Rare: atrial arrhythmia, bradycardia, AV block.

Central and Peripheral Nervous System:

Common: Movement disorders (such as extrapyramidal symptoms and gait abnormalities), paraesthesia;

Uncommon: migraine;

Rare: Coma, muscle contractions involuntary. Also reported were signs and symptoms associated with serotonin syndrome: in some cases associated with concomitant use of serotonergic drugs, that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia.

Endocrinological:

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

Gastrointestinal:

Common: Constipation;

Uncommon: Appetite increased;

Rare: Pancreatitis

Hearing/Vestibular:

Common: Tinnitus

Haematopoietic:

Uncommon: Purpura;

Rare: Altered platelet function, abnormal bleeding (such as epistaxis, gastrointestinal bleeding or haematuria), leukopenia, thrombocytopenia, increased coagulation times.

Laboratory Changes:

Rare: Abnormal clinical laboratory results.

Liver/Biliary:

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

Metabolic/Nutritional:

Rare: Hyponatraemia, increased serum cholesterol, hyperglycaemia.

Musculoskeletal:

Uncommon: Arthralgia, muscle cramps;

Rare: Vasculitis.

Psychiatric:

Uncommon: Depressive symptoms, euphoria, hallucination

Rare: Aggressive reaction, psychosis, manic reaction, neuroleptic malignant syndrome.

Respiratory:

Rare: Bronchospasm

Skin:

Uncommon: Alopecia, pruritus;

Rare: Angioedema, photosensitivity skin reaction, rare reports of serious exfoliative skin disorders (eg. Stevens-Johnson syndrome and epidermal necrolysis)

Urinary:

Uncommon: urinary incontinence;

Rare: Face oedema

Vision:

Uncommon: Eye pain;

Rare: Visual field defect.

Other:

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

Interactions

Monoamine Oxidase Inhibitors - See *Contraindications and Warnings and Precautions*.

Pimozide - Increased pimozide levels have been demonstrated in a study of single low dose pimozide (2 mg) with sertraline coadministration. 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.

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.

Lithium - In placebo-controlled trials 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 medications, such as lithium, which may act via serotonergic mechanisms, 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, 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.

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

Other Serotonergic Drugs - (see *Warnings and Precautions*)

St John's Wort - (see *Warnings and Precautions*)

Protein Bound Drugs - Since sertraline is bound to plasma proteins, the potential of sertraline to interact with other plasma protein bound drugs should be borne in mind. However, in three formal interaction studies with diazepam, tolbutamide, and warfarin, respectively, sertraline was not shown to have significant effects on the protein binding of the substrate (see subsections *Warfarin*, *CNS Active Drugs* and *Hypoglycaemic Drugs*).

Warfarin - Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Cimetidine - Co-administration of sertraline with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of this change is unknown.

CNS active drugs - Co-administration of sertraline 200 mg daily with diazepam resulted in small, statistically significant changes in some pharmacokinetic parameters. The clinical significance of these changes is unknown.

Hypoglycaemic drugs - Co-administration of sertraline 200 mg daily with tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters. The clinical significance of these changes is unknown.

Sertraline 200 mg daily did not affect the pharmacokinetics of glibenclamide.

Patients receiving biguanides should monitor their blood glucose carefully when sertraline is introduced.

Atenolol - Sertraline had no effect on the beta-adrenergic blocking ability of atenolol.

Digoxin - Sertraline 200 mg daily did not change serum digoxin levels or digoxin renal clearance.

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

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

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

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

Drugs Metabolised by Cytochrome P450 (CYP) 2D6 - There is variability among antidepressants in the extent to which they inhibit the activity of isozyme cytochrome CYP 2D6. The clinical significance of this depends on the extent of the inhibition and the therapeutic index of the co-administered drug. CYP 2D6 substrates with a narrow therapeutic index include TCAs and class 1C antiarrhythmics such as propafenone and flecainide. In formal interaction studies, chronic dosing with sertraline 50 mg daily showed minimal elevation (mean 23-37%) of steady state desipramine plasma levels (a marker of CYP 2D6 isoenzyme activity).

Drugs Metabolised by Other CYP Enzymes (CYP 3A3/4, CYP 2C9, CYP 2C19, CYP 1A2) -

CYP 3A3/4 - *In vivo* interaction studies have demonstrated that chronic administration of sertraline 200 mg daily does not inhibit the CYP 3A3/4 mediated 6- β hydroxylation of endogenous cortisol or the metabolism of carbamazepine or terfenadine. In addition, the chronic administration of sertraline 50 mg daily does not inhibit the CYP 3A3/4 mediated metabolism of alprazolam. The data suggest that sertraline is not a clinically relevant inhibitor of CYP 3A/34.

CYP 2C9 - The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of tolbutamide, phenytoin and warfarin suggests that sertraline is not a clinically relevant inhibitor of CYP 2C9. (*see subsections Hypoglycaemic Drugs, Phenytoin and Warfarin*).

CYP 2C19 - The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of diazepam suggests that sertraline is not a clinically relevant inhibitor of CYP 2C19. (*see subsection CNS Active Drugs*).

CYP 1A2 - *In vitro* studies indicate that sertraline has little or no potential to inhibit CYP 1A2.

Overdosage

On the evidence available, sertraline has a wide margin of safety in overdose. An overdose of sertraline alone of up to 13.5 g has been reported. Deaths have been reported involving overdoses of sertraline, primarily in combination with other drugs and/or alcohol. Therefore, any overdosage should be treated aggressively. Symptoms of overdose include serotonin-mediated side effects such as somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness. Less frequently reported was coma.

There are no specific antidotes to sertraline. Establish and maintain an airway and ensure adequate oxygenation and ventilation, if necessary. 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 and vital sign monitoring is recommended along with general symptomatic and supportive

measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

Pharmaceutical Precautions

Store below 25 °C.

Medicine Classification

Prescription Medicine.

Package Quantities

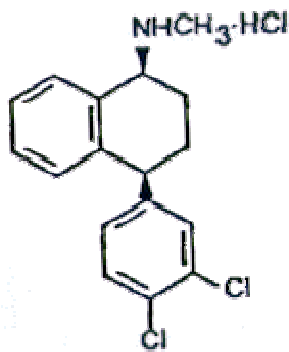
SETRONA 50 mg Tablets: Blister packs of 30 tablets.

SETRONA 100 mg Tablets: Blister packs of 30 tablets.

Shelf life: 36 months

Further Information

Sertraline hydrochloride is a naphthylamine derivative, having the following chemical name: (1*S*,*cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. It has a molecular weight of 342.7.



Preclinical Safety Data

Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective. Sertraline has also been shown to be devoid of mutagenic effects.

Other ingredients

SETRONA tablets also contain: Calcium hydrogen phosphate, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate and magnesium stearate

Coating: Opadry OY-S-58910 contains hypromellose, titanium dioxide, macrogol and talc.

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Date of Preparation

05 December 2011