# SERTRALINE

# EXULTEN®

## 50 mg FILM-COATED TABLET

## ANTIDEPRESSANT / SELECTIVE SEROTONIN REUPTAKE INHIBITOR

**FORMULATION**
Each film-coated tablet contains:
Sertraline (as hydrochloride)……50 mg

**PRODUCT DESCRIPTION**
Sertraline HCl (Exulten) is a white, capsule-shaped film-coated tablet, bisected on one side.

**PHARMACOLOGY**
Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) antidepressant. Its mechanism of action is presumed to be linked to its inhibition of the central nervous system (CNS) neuronal uptake of serotonin (5HT). At clinical doses, sertraline blocks the uptake of serotonin into human platelets.

*In vitro* studies in animals suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic ($\alpha_1$, $\alpha_2$, $\beta$), cholinergic, gamma aminobutyric acid (GABA), dopaminergic, histaminergic, serotonergic (5HT1A, 5HT1B, 5HT2), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs. The chronic use of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder (MDD). Sertraline does not inhibit monoamine oxidase.

**PHARMACOKINETICS**
Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg. Its peak plasma concentration ($C_{max}$) occurs between 4.5 to 8.4 hours after ingestion of 50 to 200 mg once a day for 14 days. The average terminal half-life ($t_{1/2}$) of plasma sertraline is about 26 hours. Steady-state concentrations of sertraline are achieved after approximately one week of once-a-day dosing. Consistent with the terminal elimination $t_{1/2}$, there is an approximately two-fold accumulation, compared to a single dose, with repeated sertraline dosing over a 50 to 200 mg dose range. Sertraline's area under the curve (AUC) was slightly increased when sertraline was administered with food but the $C_{max}$ was 25% greater, while the time to reach peak plasma concentration ($T_{max}$) decreased from eight hours post-dosing to 5.5 hours.

Approximately 98% of the circulating drug is bound to plasma proteins. Animal studies showed that sertraline has a large apparent volume of distribution.

Sertraline undergoes extensive first-pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination $t_{1/2}$ of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. Desmethylsertraline exhibits time-related, dose-dependent increases in AUC (0-24 hour), $C_{max}$ and $C_{min}$, with about a 5 to 9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity**.** About 40 to 45% of the administered radioactivity was recovered in the urine in nine days; unchanged sertraline was not detectable in the urine. For the same period, about 40 to 45% of the administered radioactivity was accounted for in the feces, including 12 to 14% unchanged sertraline.

**Special Population:**
***Hepatic Impairment:*** Sertraline's clearance was reduced in patients with chronic mild liver impairment (Child-Pugh score of 5 to 6 and 7 to 8) who received 50 mg per day of sertraline for 21 days, resulting in approximately 3-fold greater exposure compared with age-matched volunteers with no hepatic impairment; the exposure to desmethylsertraline was approximately 2-fold greater**.** No significant differences in plasma protein binding were observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. A lower or less frequent dose should be used in patients with liver impairment.

***Renal Impairment:*** In patients with mild to moderate ($CL_{cr}$ = 30 to 60 mL/min), moderate to severe ($CL_{cr}$= 10 to 29 mL/min) or severe (receiving hemodialysis) renal impairment, the pharmacokinetics and protein binding of sertraline 200 mg per day for 21 days were not altered compared with age-matched patients with no renal impairment. Sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment.

***Age:*** Sertraline's plasma clearance is about 40% lower in elderly patients compared with younger individuals. Decreased desmethylsertraline clearance is seen in older males but not in older females.

***Children:*** The pharmacokinetics of sertraline was evaluated in children with a DSM-III-R diagnosis of MDD or obsessive-compulsive disorder**.** During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg per day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg per day, mean sertraline $AUC_{0-24\,hr}$, mean $C_{max}$, and mean $t_{1/2}$ were 3,107 ng.hr/mL, 165 ng/mL, 26.2 hours, respectively, in patients 6 to 12 years old. The 13 to 17 years old group exhibited a mean sertraline $AUC_{0-24\,hr}$ of 2,296 ng.hr/mL, mean $C_{max}$ of 123 ng/mL, and mean $t_{1/2}$ of 27.8 hours. The higher plasma levels in the 6 to 12 years old group were largely attributable to patients with lower body weights. No gender-associated differences were observed. Both the 6 to 12 years old and 13 to 17 years old showed 22% lower $AUC_{0-24\,hr}$ and $C_{max}$ values when plasma concentration was adjusted for weight relative to adults. Reduced doses may be advisable for pediatric patients (particularly very young patients) given their lower body weights in order to avoid excessive plasma levels.

**INDICATIONS**
***In adults,*** sertraline is indicated for the treatment of:
- Major depressive disorder (MDD)
- Obsessive-compulsive disorder (OCD)
- Panic disorder with or without agoraphobia
- Posttraumatic stress disorder (PTSD)
- Premenstrual dysphoric disorder (PMDD)
- Social anxiety disorder or social phobia

***In children (6 to 17 years old),*** sertraline is indicated for the treatment of Obsessive Compulsive Disorder (OCD).

**DOSAGE AND ADMINISTRATION**

**Adult Dose:**

| Recommended Sertraline Adult Oral Dose | |
|---|---|
| *To be administered once daily in the morning or evening, with or without food.* | |
| **INITIAL TREATMENT** | **MAINTENANCE / CONTINUATION / EXTENDED TREATMENT** |
| **Major Depressive Disorder and Obsessive-Compulsive Disorder** | |
| **Initial Dose:** 50 mg once a day;<br>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 per day**.** Changes in dose should not be made more frequently than once a week given the 24-hour elimination $t_{1/2}$ of sertraline.<br><br>The onset of therapeutic effect may be seen within seven days. However, longer periods are usually necessary to show therapeutic response, particularly in OCD. | **Major Depressive Disorder:**<br>Longer-term treatment may also be appropriate for prevention of recurrence of Major Depressive Episode (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 six months to ensure they are free from symptoms.<br><br>**Obsessive-Compulsive Disorder:**<br>It is generally agreed that OCD and panic disorder require several months or longer of sustained pharmacological therapy beyond response to initial treatment.<br><br>It is not known whether the dose of sertraline needed for maintenance treatment is identical to the dose needed to achieve an initial response. |
| **Panic Disorder, Posttraumatic Stress Disorder, and Social Anxiety Disorder** | |
| **Initial Dose**: 25 mg once a day;<br><br>After one week, the dose should be increased to 50 mg once a day. This dosage regimen has been shown to reduce the frequency of early treatment emergent side effects characteristic of panic disorder**.**<br><br>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 per day**.** Changes in dose should not be made more frequently than once a week given the 24-hour elimination half-life of sertraline.<br><br>The onset of therapeutic effect may be seen within seven days. However, longer periods are usually necessary to show therapeutic response. | **Panic Disorder:**<br>Continued treatment should be evaluated regularly, as relapse prevention has not been shown for these disorders.<br><br>**Posttraumatic Stress Disorder:**<br>It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment.<br><br>It is not known whether the dose of sertraline needed for maintenance treatment is identical to the dose needed to achieve an initial response.<br><br>**Social Anxiety Disorder:**<br>Social anxiety disorder is a chronic condition that may require several months or longer of sustained pharmacological therapy beyond response to initial treatment.<br><br>Dosage adjustments should be made to maintain patients on the lowest effective dose. |

| Recommended Sertraline Adult Oral Dose | |
|---|---|
| *To be administered once daily in the morning or evening, with or without food.* | |
| **INITIAL TREATMENT** | **MAINTENANCE / CONTINUATION EXTENDED TREATMENT** |
| **Premenstrual Dysphoric Disorder** | |
| **Initial Dose:**<br>50 mg once a day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.<br><br>Patients not responding to a 50 mg per day dose may benefit from dose increases (at 50 mg increments/menstrual cycle) up to 150 mg per day when dosing daily throughout the menstrual cycle, or 100 mg per day when dosing during the luteal phase of the menstrual cycle.<br><br>If a 100 mg per day dose has been established with luteal phase dosing, a 50 mg per day titration step for three days should be utilized at the beginning of each luteal phase dosing period. | The efficacy of sertraline in long-term use, i.e., for more than three menstrual cycles, has not been systematically evaluated in controlled trials. However, as women commonly report that symptoms worsen with age until relieved by the onset of menopause, it is reasonable to consider continuation of a responding patient.<br><br>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 dose. |
| Patients should be periodically reassessed to determine the need for maintenance treatment.<br>Dosage during long-term therapy should be kept at the lowest effective dose,<br>with subsequent adjustment depending on therapeutic response. | |
| Or, as prescribed by a physician. | |

**Pediatric Dose:**

| Pediatric Dose in Obsessive-Compulsive Disorder | |
|---|---|
| **Age Group (years)** | **Recommended Initial Dose** |
| **6 to 12** | 25 mg once a day;<br><br>The dose may be increased to<br>50 mg once a day after one week. |
| **13 to 17** | 50 mg once daily |
| Subsequent doses may be increased in case of less than the desired response in 50 mg increments over a period of some weeks, as needed. The maximum dose is 200 mg per day**.** Given the 24-hour elimination half-life of sertraline, dose changes should not occur at intervals of less than one week.<br><br>For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. | |
| Or, as prescribed by a physician. | |

**Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI):**
At least 14 days should elapse between discontinuation of a MAOI and initiation of therapy with sertraline. In addition, at least 14 days should be allowed after stopping sertraline before starting a MAOI.

**Discontinuing Treatment:**
- Closely monitor patients for symptoms associated with discontinuation of sertraline and other SSRIs and selective norepinephrine reuptake inhibitors (SNRIs).
- Gradual dose reduction rather than abrupt cessation of treatment is recommended whenever possible.
- Consider resumption of previously prescribed dose if intolerable symptoms occur after a decrease in the dose or upon discontinuation of treatment. Reduction of the dose may be continued but at a more gradual rate.

**CONTRAINDICATIONS**
- Hypersensitivity to sertraline hydrochloride or to any ingredient in the product.
- Concomitant use with MAOIs and pimozide.

**WARNINGS AND PRECAUTIONS**

**Suicidality and Antidepressant Drugs**

**Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of sertraline or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond 24 years old; there was a reduction in risk with antidepressants compared to placebo in adults 65 years and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Sertraline is not approved for use in pediatric patients except for patients with obsessive-compulsive disorder (OCD).**

**Clinical Worsening and Suicide Risk**
Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality**.**

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

**Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.**

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

**Screening for Bipolar Disorder**
Bipolar disorder may present initially as a Major Depressive Episode (MDE). Treating an MDE with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder**.** Adequately screen patients with depressive symptoms if they are at risk for bipolar disorder before starting antidepressant treatment. Include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, depression) during such screening. Sertraline is not approved for use in treating bipolar depression.

**Serotonin Syndrome or neuroleptic malignant syndrome (NMS)**
SSRIs such as sertraline, and SNRIs can cause potentially life-threatening serotonin syndrome or NMS-like reactions, particularly when taken together with serotonergic drugs (including triptans and fentanyl), with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Characteristic symptoms of serotonin syndrome 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, diarrhea). Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

**Activation of Mania/Hypomania**
Mania or hypomania has been reported in patients taking sertraline.

**Seizures**
Use sertraline cautiously in patients with seizure disorder**.**

**Interference with Cognitive and Motor Performance**
Sertraline does not cause sedation or interfere with 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**.**

**Potential Interaction with MAOIs**
**Cases of serious sometimes fatal reactions have been reported in patients receiving sertraline, an SSRI, in combination with a MAOI. Symptoms of a drug interaction between an SSRI and a MAOI 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. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on a MAOI; some cases presented with features resembling NMS. Thus, sertraline should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping sertraline before starting a MAOI.**

**Weight Loss**
Sertraline may cause significant weight loss which may be undesirable for some patients.

**Diabetes / Loss of Glycemic Control**
Cases of new onset diabetes mellitus have been reported in patients receiving SSRIs including sertraline. Loss of glycemic control including both hyperglycemia and hypoglycemia has also been reported in patients with and without pre-existing diabetes. Thus, patients should be monitored for signs and symptoms of glucose fluctuations. Diabetic patients especially should have their glycemic control carefully monitored since their dosage of insulin and/or concomitant oral hypoglycemic drug may need to be adjusted.

**Weak Uricosuric Effect**
Sertraline hydrochloride may decrease serum uric acid. The clinical significance of this weak uricosuric effect is unknown.

**Hyponatremia**
Hyponatremia may occur as a result of treatment with SSRIs, including sertraline, and SNRIs. This hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium 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.

**Abnormal Bleeding**
SSRIs, including sertraline, and SNRIs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies have shown an association between the use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to the use of SSRIs and SNRIs have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of sertraline and NSAID, aspirin, or other drugs that affect coagulation.

**Platelet Function**
Sertraline may cause alteration of platelet function and/or abnormal laboratory results. Although abnormal bleeding or purpura has also been reported with sertraline use, the causative role of sertraline is unclear**.**

**Use in Patients with Concomitant Illness**
Use sertraline cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

**Discontinuation of Sertraline Treatment**
Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania have been associated with discontinuation of sertraline, particularly when abrupt, and other SSRIs and SNRIs.

**INTERACTIONS WITH OTHER MEDICAMENTS**

- **Monoamine oxidase inhibitors: Concomitant use is contraindicated.**

**Irreversible (non-selective) MAOIs (selegiline)**
Sertraline should not be used in combination with irreversible (non-selective) MAOIs such as selegiline. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible (non-selective) MAOI. Sertraline must be discontinued for at least seven days before starting treatment with an irreversible (non-selective) MAOI.

**Reversible, selective MAO-A inhibitor (moclobemide)**
Due to risk of serotonin syndrome, the combination of sertraline with a reversible and selective MAOI, such as moclobemide, is not recommended. After 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 seven 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 a MAOI and started on sertraline, or have recently had sertraline therapy discontinued prior to initiation of a MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling NMS, seizures, and death.

- **Pimozide:** Coadministration of single low dose pimozide 2 mg with sertraline was associated with a mean increase in pimozide AUC and $C_{max}$ of about 40%, but was not associated with any changes in electrocardiogram. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, **concomitant use of sertraline and pimozide is contraindicated.**

- **CNS depressants and alcohol:** The coadministration of sertraline 200 mg per day did not potentiate the effects of alcohol, carbamazepine, or haloperidol on cognitive and psychomotor performance in healthy subjects; however, the concomitant use of sertraline and alcohol is not recommended.

Chronic use of sertraline 200 mg per day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, it is recommended that plasma phenytoin concentrations be monitored after initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant drugs. Also, coadministration of phenytoin may cause a reduction of sertraline plasma levels.

- **Serotonergic drugs:** Based on the mechanism of action of SNRIs and SSRIs, including sertraline, and the potential for serotonin syndrome, caution is advised when SNRIs and SSRIs, including sertraline, are coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid, lithium, tramadol, or St. John's Wort. The concomitant use of sertraline with other SSRIs, SNRIs or tryptophan is not recommended.

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

- **Lithium:** Coadministration of sertraline with lithium did not significantly alter lithium pharmacokinetic, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When coadministering sertraline with lithium, which may act via serotonergic mechanisms, it is recommended that plasma lithium levels be monitored after initiation of sertraline therapy with appropriate adjustments to the lithium dose.

- **Protein-bound drugs:** Since sertraline is tightly bound to plasma protein, the administration of sertraline to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound sertraline by other tightly bound drugs.

In a study comparing prothrombin time AUC (0-120 hour) after dosing with warfarin, before and after 21 days of dosing with either sertraline or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for sertraline compared to a 1% decrease for placebo. The normalization of prothrombin time for the sertraline group was delayed compared to the placebo group. The clinical significance of this change is unknown. Thus, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

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

Coadministration of sertraline with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Thus, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

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

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

- **CNS-active drugs (diazepam): C**oadministration of sertraline with intravenous diazepam resulted in a small, statistically significant changes in some pharmacokinetic parameters. The clinical significance of these changes is unknown.

- **Hypoglycemic drugs (tolbutamide, glibenclamide, biguanides):** Coadministration of sertraline with tolbutamide resulted in a small, statistically significant changes in some pharmacokinetic parameters. The clinical significance of these changes is unknown.

Sertraline did not affect the pharmacokinetics of glibenclamide.

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

- **Drugs metabolized by cytochrome P450 (CYP) 2D6:** Sertraline may act as a mild-moderate inhibitor of CYP 2D6. Chronic dosing with sertraline 50 mg per day showed moderate elevation (mean 23%-37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isozyme activity). Clinically relevant interactions may occur with other CYP 2D6 substrates with a narrow therapeutic index such as class 1C antiarrhythmics (propafenone, flecainide, tricyclic antidepressants and typical antipsychotics), particularly at higher sertraline dose levels.

- **Drugs metabolized by other CYP enzymes (CYP 3A4, CYP 2C9, CYP 2C19, CYP 1A2):** Sertraline does not act as an inhibitor of CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2 to a clinically significant degree. This has been 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.

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

- **Digoxin:** Sertraline did not change serum digoxin levels or digoxin renal clearance.

- **Microsomal enzyme induction:** Sertraline was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life after administration of 200 mg per day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

**Other Interaction:**

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

**STATEMENT ON USAGE FOR HIGH RISK GROUPS**

**PREGNANCY AND LACTATION**

**Pregnancy**
*Pregnancy Category C.* There are no adequate and well-controlled studies in pregnant women. Sertraline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Pregnancy-Nonteratogenic Effects**
Neonates exposed to sertraline and other SSRIs or SNRIs, late in the third trimester of pregnancy have developed complications requiring prolonged hospitalization, respiratory support and tube feeding which can arise immediately upon delivery**.** These complications which include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In some cases, the clinical picture is consistent with serotonin syndrome. Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN).

When treating a pregnant woman with sertraline during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment. The physician may consider tapering sertraline in the third trimester**.**

**Labor and Delivery**
The effect of sertraline on labor and delivery is unknown.

**Lactation**
It is not known if sertraline or its metabolites is excreted in human milk. Exercise caution when sertraline is administered to a breastfeeding woman.

**INFANTS AND CHILDREN**
Sertraline should not be used in the treatment of children and adolescents under 18 years old, except for patients with OCD aged 6 to 17 years old. Suicide-related behaviors (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behavior 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, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development are lacking. Physicians must monitor pediatric patients on long term treatment for abnormalities in these body systems.

**ELDERLY**
No overall differences in efficacy or adverse effects are observed in geriatric patients relative to younger patients. The elderly should be dosed carefully, as they may be more at risk for hyponatremia.

**ADVERSE EFFECTS/UNDESIRABLE EFFECTS**
**Body as a whole:** Fatigue, pain, back pain, malaise, asthenia, fever, rigors

**Cardiovascular:** Hot flushes, flushing, palpitation, vasodilation, chest pain, hypertension, aggravated hypertension, pulmonary hypertension, hypotension, postural hypotension, tachycardia, ventricular tachycardia (including *torsades de pointes*-type arrhythmia), bradycardia, postural dizziness, edema (periorbital, peripheral, dependent, generalized, face), peripheral ischemia, syncope, precordial chest pain, substernal chest pain, myocardial infarction, cerebrovascular disorder, AV block, atrial arrhythmias, QT-interval prolongation

**Endocrine/Metabolic:** Anorexia; thirst; increased appetite; increased weight; hypoglycemia; hyperglycemia; diabetes mellitus; increased total cholesterol, triglycerides; decreased serum uric acid; hypothyroidism; hyperprolactinemia; ejaculation failure; increased/decreased libido; impotence; priapism

**Gastrointestinal:** Dry mouth, aggravated tooth caries, gum hyperplasia, hiccups, increased saliva, dyspepsia, dysphagia, abdominal pain, vomiting, constipation, esophagitis, gastroenteritis, stomatitis, aphthous stomatitis, gastritis, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, melena, glossitis, eructation, diarrhea/loose stools, tenesmus, colitis, diverticulitis, fecal incontinence, rectum hemorrhage, pancreatitis

**Hematological:** Anemia, aplastic anemia, agranulocytosis, pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, increased coagulation time

**Hepatic:** Abnormal hepatic function, asymptomatic elevations in serum transaminases, increased bilirubin, hepatomegaly, hepatitis, jaundice, liver failure

**Musculoskeletal:** Myalgia, arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness

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**Respiratory:** Rhinitis, coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis, hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis, yawning

**Special senses:** Abnormal vision, mydriasis, glaucoma, nystagmus, ptosis, exophthalmos, anterior chamber eye hemorrhage, blindness, optic neuritis, cataract, tinnitus, conjunctivitis, eye pain, abnormal accommodation, xerophthalmia, photophobia, diplopia, oculogyric crisis, abnormal lacrimation, scotoma, visual field defect, tongue edema, tongue ulceration, hyperacusis, labyrinthine disorder, earache

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Available evidence suggests that sertraline has a wide margin of safety in overdosage. The largest known ingestion was 13.5 grams in a patient who took sertraline hydrochloride alone and subsequently recovered. Deaths have been reported involving sertraline overdosage, primarily in combination with other drugs and/or alcohol. Thus, any overdosage should be medically treated aggressively**.**

The most common signs and symptoms associated with non-fatal sertraline overdosage were somnolence, vomiting, tachycardia, nausea, dizziness, agitation, and tremor**.** Other important adverse events reported with sertraline overdosage (single or multiple drugs) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor, and syncope.

There are no specific antidotes to sertraline. Treatment should consist of general measures employed in the management of overdosage with any antidepressant. Ensure adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if done soon after ingestion, or in symptomatic patients. Activated charcoal should be administered. Due to large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, consider the possibility of multiple drug involvement.

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**AVAILABILITY**
Blister Foil x10's (Box of 30's) **-** DR-XY34937

**CAUTION**
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Trusted Quality Healthcare

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
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Metro Manila, Philippines

**P300000017474** Date of First Authorization: September 15, 2008 Date of revision: July 2018 *Reg. IPOPHIL

accordingly**.**

**Potential Interaction with MAOIs**
**Cases of serious sometimes fatal reactions have been reported in patients receiving sertraline, an SSRI, in combination with a MAOI. Symptoms of a drug interaction between an SSRI and a MAOI 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. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on a MAOI; some cases presented with features resembling NMS. Thus, sertraline should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping sertraline before starting a MAOI.**

**Weight Loss**
Sertraline may cause significant weight loss which may be undesirable for some patients.

**Diabetes / Loss of Glycemic Control**
Cases of new onset diabetes mellitus have been reported in patients receiving SSRIs including sertraline. Loss of glycemic control including both hyperglycemia and hypoglycemia has also been reported in patients with and without pre-existing diabetes. Thus, patients should be monitored for signs and symptoms of glucose fluctuations. Diabetic patients especially should have their glycemic control carefully monitored since their dosage of insulin and/or concomitant oral hypoglycemic drug may need to be adjusted.

**Weak Uricosuric Effect**
Sertraline hydrochloride may decrease serum uric acid. The clinical significance of this weak uricosuric effect is unknown.

**Hyponatremia**
Hyponatremia may occur as a result of treatment with SSRIs, including sertraline, and SNRIs. This hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium 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.

**Abnormal Bleeding**
SSRIs, including sertraline, and SNRIs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies have shown an association between the use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to the use of SSRIs and SNRIs have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of sertraline and NSAID, aspirin, or other drugs that affect coagulation.

**Platelet Function**
Sertraline may cause alteration of platelet function and/or abnormal laboratory results. Although abnormal bleeding or purpura has also been reported with sertraline use, the causative role of sertraline is unclear**.**

**Use in Patients with Concomitant Illness**
Use sertraline cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

**Discontinuation of Sertraline Treatment**
Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania have been associated with discontinuation of sertraline, particularly when abrupt, and other SSRIs and SNRIs.

**INTERACTIONS WITH OTHER MEDICAMENTS**

• **Monoamine oxidase inhibitors: Concomitant use is contraindicated.**

**Irreversible (non-selective) MAOIs (selegiline)**
Sertraline should not be used in combination with irreversible (non-selective) MAOIs such as selegiline. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible (non-selective) MAOI. Sertraline must be discontinued for at least seven days before starting treatment with an irreversible (non-selective) MAOI.

**Reversible, selective MAO-A inhibitor (moclobemide)**
Due to risk of serotonin syndrome, the combination of sertraline with a reversible and selective MAOI, such as moclobemide, is not recommended. After 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 seven 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 a MAOI and started on sertraline, or have recently had sertraline therapy discontinued prior to initiation of a MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling NMS, seizures, and death.

• **Pimozide:** Coadministration of single low dose pimozide 2 mg with sertraline was associated with a mean increase in pimozide AUC and $C_{max}$ of about 40%, but was not associated with any changes in electrocardiogram. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, **concomitant use of sertraline and pimozide is contraindicated.**

• **CNS depressants and alcohol:** The coadministration of sertraline 200 mg per day did not potentiate the effects of alcohol, carbamazepine, or haloperidol on cognitive and psychomotor performance in healthy subjects; however, the concomitant use of sertraline and alcohol is not recommended.

Chronic use of sertraline 200 mg per day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, it is recommended that plasma phenytoin concentrations be monitored after initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant drugs. Also, coadministration of phenytoin may cause a reduction of sertraline plasma levels.

• **Serotonergic drugs:** Based on the mechanism of action of SNRIs and SSRIs, including sertraline, and the potential for serotonin syndrome, caution is advised when SNRIs and SSRIs, including sertraline, are coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid, lithium, tramadol, or St. John's Wort. The concomitant use of sertraline with other SSRIs, SNRIs or tryptophan is not recommended.

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

• **Lithium:** Coadministration of sertraline with lithium did not significantly alter lithium pharmacokinetic, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When coadministering sertraline with lithium, which may act via serotonergic mechanisms, it is recommended that plasma lithium levels be monitored after initiation of sertraline therapy with appropriate adjustments to the lithium dose.

• **Protein-bound drugs:** Since sertraline is tightly bound to plasma protein, the administration of sertraline to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound sertraline by other tightly bound drugs.

In a study comparing prothrombin time AUC (0-120 hour) after dosing with warfarin, before and after 21 days of dosing with either sertraline or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for sertraline compared to a 1% decrease for placebo. The normalization of prothrombin time for the sertraline group was delayed compared to the placebo group. The clinical significance of this change is unknown. Thus, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

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

Coadministration of sertraline with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Thus, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

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

• **Cimetidine:** Coadministration of sertraline with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of this change is unknown.

• **CNS-active drugs (diazepam):** Coadministration of sertraline with intravenous diazepam resulted in a small, statistically significant changes in some pharmacokinetic parameters. The clinical significance of these changes is unknown.

• **Hypoglycemic drugs (tolbutamide, glibenclamide, biguanides):** Coadministration of sertraline with tolbutamide resulted in a small, statistically significant changes in some pharmacokinetic parameters. The clinical significance of these changes is unknown.

Sertraline did not affect the pharmacokinetics of glibenclamide.

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

• **Drugs metabolized by cytochrome P450 (CYP) 2D6:** Sertraline may act as a mild-moderate inhibitor of CYP 2D6. Chronic dosing with sertraline 50 mg per day showed moderate elevation (mean 23%-37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isozyme activity). Clinically relevant interactions may occur with other CYP 2D6 substrates with a narrow therapeutic index such as class 1C antiarrhythmics (propafenone, flecainide, tricyclic antidepressants and typical antipsychotics), particularly at higher sertraline dose levels.

• **Drugs metabolized by other CYP enzymes (CYP 3A4, CYP 2C9, CYP 2C19, CYP 1A2):** Sertraline does not act as an inhibitor of CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2 to a clinically significant degree. This has been 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.

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

• **Digoxin:** Sertraline did not change serum digoxin levels or digoxin renal clearance.

• **Microsomal enzyme induction:** Sertraline was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life after administration of 200 mg per day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

**Other Interaction:**

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

**STATEMENT ON USAGE FOR HIGH RISK GROUPS**

**PREGNANCY AND LACTATION**

**Pregnancy**
*Pregnancy Category C.* There are no adequate and well-controlled studies in pregnant women. Sertraline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Pregnancy-Nonteratogenic Effects**
Neonates exposed to sertraline and other SSRIs or SNRIs, late in the third trimester of pregnancy have developed complications requiring prolonged hospitalization, respiratory support and tube feeding which can arise immediately upon delivery**.** These complications which include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In some cases, the clinical picture is consistent with serotonin syndrome. Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN).

When treating a pregnant woman with sertraline during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment. The physician may consider tapering sertraline in the third trimester**.**

**Labor and Delivery**
The effect of sertraline on labor and delivery is unknown.

**Lactation**
It is not known if sertraline or its metabolites is excreted in human milk. Exercise caution when sertraline is administered to a breastfeeding woman.

**INFANTS AND CHILDREN**
Sertraline should not be used in the treatment of children and adolescents under 18 years old, except for patients with OCD aged 6 to 17 years old. Suicide-related behaviors (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behavior 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, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development are lacking. Physicians must monitor pediatric patients on long term treatment for abnormalities in these body systems.

**ELDERLY**
No overall differences in efficacy or adverse effects are observed in geriatric patients relative to younger patients. The elderly should be dosed carefully, as they may be more at risk for hyponatremia.

**ADVERSE EFFECTS/UNDESIRABLE EFFECTS**
**Body as a whole:** Fatigue, pain, back pain, malaise, asthenia, fever, rigors

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