Size: 260 (L) x 360 (H) mm
Folding size: 30 (L) x 150 (H) mm
Drg. No. : 9917306-005

Front side

Paper 35 to 50 gsm
Carton size: 36 x 25 x 75 mm

260 mm
110 mm
150 mm
360 mm
30 mm

SERTRALINE

ZOTRAL™

50 mg Tablet
ANTIDEPRESSANT

PRODUCT NAME:
Zotral

NAME AND STRENGTH:
Sertraline Tablets 50 mg

PHARMACOLOGIC CATEGORY:
Antidepressant

PRODUCT DESCRIPTION:
Light Blue coloured, circular, biconvex, film coated tablets with a breakline on one surface.

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Sertraline Hydrochloride BP..... 50 mg

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacodynamics:
The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro studies have shown that sertraline has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, 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 administration of sertraline was found in animals to down regulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics:
Systemic Bioavailability
In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the Cmax and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.
In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and Cmax values were 114.8% and 120.6%, respectively. 90% confidence intervals (CI) were within the range of 80–125% with the exception of the upper 90% CI limit for Cmax which was 126.5%.
The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the Cmax was 25% greater, while the time to reach peak plasma concentration (Tmax) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, Tmax was slightly prolonged from 5.9 hours to 7.0 hours with food.
Metabolism: Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both in vitro biochemical and in vivo pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40–45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40–45% of the administered radioactivity was accounted for in feces, including 12–14% unchanged sertraline.
Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0–24 hour), Cmax and Cmin, with about a 5–9 fold increase in these pharmacokinetic parameters between day 1 and day 14.
Protein Binding: *In vitro protein binding studies performed with radiolabeled 3H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol.*
Pediatric Pharmacokinetics: Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6–12 years, 32 aged 13–17 years) with a DSM-III-R diagnosis of major depressive disorder or obsessive-compulsive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6–12 year old group exhibited a mean sertraline AUC (0–24 hr) of 3107 ng-hr/mL, mean Cmax of 165 ng/mL, and mean half-life of 26.2 hr. The 13–17 year old group exhibited a mean sertraline AUC (0–24 hr) of 2296 ng-hr/mL, mean Cmax of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6–12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0–24 hr) of 2570 ng-hr/mL, mean Cmax of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6–12 year olds and the 13–17 year olds showed about 22% lower AUC (0–24 hr) and Cmax values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels.
Age: Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady-state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.
Liver Disease: As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5–6 and 2 patients with Child-Pugh scores of 7–8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.
Renal Disease: Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLcr=30–60 mL/min), moderate to severe (CLcr=10–29 mL/min) or severe (receiving hemodialysis) renal impairment (N=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (N=12) with no renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment.

INDICATIONS:
Sertraline is indicated for the treatment of:
- Major depressive episodes. Prevention of recurrence of major depressive episodes.
- Panic disorder, with or without agoraphobia.
- Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years.
- Social anxiety disorder.
- Post traumatic stress disorder (PTSD).

DOSAGE AND MODE ROUTE OF ADMINISTRATION:
Initial Treatment
Dosage for Adults
Major Depressive Disorder and Obsessive-Compulsive Disorder
Sertraline treatment should be administered at a dose of 50 mg once daily.
Panic Disorder, Posttraumatic Stress Disorder and Social Anxiety Disorder
Sertraline treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily.
While a relationship between dose and effect has not been established for major depressive disorder, OCD, panic disorder, PTSD or social anxiety disorder, patients were dosed in a range of 50–200 mg/day in the clinical trials demonstrating the effectiveness of Sertraline for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of Sertraline, dose changes should not occur at intervals of less than 1 week.

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.
While a relationship between dose and effect has not been established for PMDD, patients were dosed in the range of 50–150 mg/day with dose increases at the onset of each new menstrual cycle. Patients not responding to a 50 mg/day dose may benefit from dose increases (at 50 mg increments/menstrual cycle) up to 150 mg/day when dosing daily throughout the menstrual cycle, or 100 mg/day when dosing during the luteal phase of the menstrual cycle. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilized at the beginning of each luteal phase dosing period.
Sertraline should be administered once daily, either in the morning or evening.
Dosage for Pediatric Population (Children and Adolescents)

Obsessive-Compulsive Disorder
Sertraline treatment should be initiated with a dose of 25 mg once daily in children (ages 6–12) and at a dose of 50 mg once daily in adolescents (ages 13–17).
While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25–200 mg/day in the clinical trials demonstrating the effectiveness of Sertraline for pediatric patients (6–17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. 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. Given the 24 hour elimination half-life of Sertraline, dose changes should not occur at intervals of less than 1 week.
Sertraline should be administered once daily, either in the morning or evening.
Maintenance/Continuation/Extended Treatment
Major Depressive Disorder: It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy beyond response to the acute episode. Systematic evaluation of Sertraline has demonstrated that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of initial treatment at a dose of 50–200 mg/day (mean dose of 70 mg/day). It is not known whether the dose of Sertraline needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.
Posttraumatic Stress Disorder: It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of Sertraline has demonstrated that its efficacy in PTSD is maintained for periods of up to 28 weeks following 24 weeks of treatment at a dose of 50–200 mg/day. It is not known whether the dose of Sertraline needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.
Social Anxiety Disorder: Social anxiety disorder is a chronic condition that may require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of Sertraline has demonstrated that its efficacy in social anxiety disorder is maintained for periods of up to 24 weeks following 20 weeks of treatment at a dose of 50–200 mg/day. Dosage adjustments should be made to maintain patients on the lowest effective dose and patients should be periodically reassessed to determine the need for long-term treatment.
Obsessive-Compulsive Disorder and Panic Disorder: It is generally agreed that OCD and Panic Disorder require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of continuing Sertraline for periods of up to 28 weeks in patients with OCD and Panic Disorder who have responded while taking Sertraline during initial treatment phases of 24 to 52 weeks of treatment at a dose range of 50–200 mg/day has demonstrated a benefit of such maintenance treatment. It is not known whether the dose of Sertraline needed for maintenance treatment is identical to the dose needed to achieve an initial response. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.
Premenstrual Dysphoric Disorder: The effectiveness of Sertraline in long-term use, that is, for more than 3 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. 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.
Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat
Psychiatric Disorders: At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with Sertraline. Conversely, at least 14 days should be allowed after stopping Sertraline before starting an MAOI intended to treat psychiatric disorders
Use of Sertraline with Other MAOIs Such as Linezolid or Methylene Blue
Do not start Sertraline in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered.
In some cases, a patient already receiving Sertraline therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, Sertraline should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Sertraline may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.
The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with Sertraline is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use.

Special Populations
Dosage for Hepatically Impaired Patients
The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.

Treatment of Pregnant Women during the Third Trimester
Neonates exposed to Sertraline and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with Sertraline during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.
Discontinuation of Treatment with Sertraline: Symptoms associated with discontinuation of Sertraline and other SSRIs and SNRIs, have been reported. Patients should be monitored for these symptoms when discontinuing treatment. 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.
Sertraline Oral Concentrate: Sertraline Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. Sertraline Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of Sertraline Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix Sertraline Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for patients with latex sensitivity, as the dropper dispenser contains dry natural rubber.

CONTRAINDICATIONS &PRECAUTION(S), WARNING(S):
All Dosage Forms of Sertraline
The use of MAOIs intended to treat psychiatric disorders with Sertraline or within 14 days of stopping treatment with Sertraline is contraindicated because of an increased risk of serotonin syndrome. The use of Sertraline within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.
Starting Sertraline in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.
Concomitant use in patients taking pimozide is contraindicated.
Sertraline is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients in Sertraline.

PRECAUTIONS & WARNINGS:
Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behaviour, 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 a 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. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behaviour (suicidality) in children, adolescents, and young adults (ages 18–24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term 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 with antidepressants compared to placebo in adults aged 65 and older.
Screening Patients for 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 an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Sertraline is not approved for use in treating bipolar depression.

Serotonin Syndrome
The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Sertraline, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, and incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Patients should be monitored for the emergence of serotonin syndrome.
The concomitant use of Sertraline with MAOIs intended to treat psychiatric disorders is contraindicated. Sertraline should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking Sertraline. Sertraline should be discontinued before initiating treatment with the MAOI.
If concomitant use of Sertraline with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.
Treatment with Sertraline and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including Sertraline may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

General
Activation of Mania/Hypomania
During premarketing testing, hypomania or mania occurred in approximately 0.4% of Sertraline (sertraline hydrochloride) treated patients.

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, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.
Seizure: Sertraline has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with Sertraline in the development program for major depressive disorder. However, 4 patients out of approximately 1800 (220<18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures, representing a crude incidence of 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. Accordingly, Sertraline should be introduced with care in patients with a seizure disorder.
***Discontinuation of Treatment with Sertraline*:** During marketing of Sertraline and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors),

PHARMACODE READING DIRECTION

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, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Sertraline. 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.

Abnormal Bleeding: SSRIs and SNRIs, including Sertraline, may increase the risk of bleeding events ranging from ecchymoses, hematomas, epistaxis, petechiae, and gastrointestinal haemorrhagee to life-threatening haemorrhagee. Concomitant use of aspirin, nonsteroidal anti inflammatory drugs, warfarin, and other anticoagulants or other drugs known to affect platelet function may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding.

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

Weak Uricosuric Effect: Sertraline (sertraline hydrochloride) is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Use in Patients with Concomitant Illness: Clinical experience with Sertraline in patients with certain concomitant systemic illness is limited. Caution is advisable in using Sertraline in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received Sertraline in double-blind trials were evaluated and the data indicate that Sertraline is not associated with the development of significant ECG abnormalities.

Sertraline administered in a flexible dose range of 50 to 200 mg/day (mean dose of 89 mg/day) was evaluated in a post-marketing, placebo-controlled trial of 372 randomized subjects with a DSM-IV diagnosis of major depressive disorder and recent history of myocardial infarction or unstable angina requiring hospitalization. Exclusions from this trial included, among others, patients with uncontrolled hypertension, need for cardiac surgery, history of CABG within 3 months of index event, severe or symptomatic bradycardia, non-atherosclerotic cause of angina, clinically significant renal impairment (creatinine > 2.5 mg/dl), and clinically significant hepatic dysfunction. Sertraline treatment initiated during the acute phase of recovery (within 30 days post-MI or post-hospitalization for unstable angina) was indistinguishable from placebo in this study on the following week 16 treatment endpoints: left ventricular ejection fraction, total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, CHF, MI, tachycardia, bradycardia, and changes in BP), and major cardiovascular events involving death or requiring hospitalization (for MI, CHF, stroke, or angina).

Sertraline is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, Cmax and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.

Since Sertraline is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetic results, there is no need for dosage adjustment in patients with renal impairment.

Interference with Cognitive and Motor Performance: In controlled studies, Sertraline did not cause sedation and did not interfere with psychomotor performance.

Hyponatraemia: Hyponatraemia may occur as a result of treatment with SSRIs and SNRIs, including Sertraline. In many cases, this hyponatraemia 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 hyponatreamia with SSRIs and SNRIs. Also, patients taking diuretics or who is otherwise volume depleted may be at greater risk. Discontinuation of Sertraline should be considered in patients with symptomatic hyponatreamia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatreamia 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.

Platelet Function

There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking Sertraline. While there have been reports of abnormal bleeding or purpura in several patients taking Sertraline, it is unclear whether Sertraline had a causative role.

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Sertraline and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions: is available for Sertraline. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Sertraline.

PREGNANCY AND LACTATION:

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

Lactation: It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sertraline is administered to a nursing woman.

INTERACTIONS:

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins

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

In a study comparing prothrombin time AUC (0–120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either Sertraline (50–200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for Sertraline compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the Sertraline group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when Sertraline therapy is initiated or stopped.

Cimetidine: In a study assessing disposition of Sertraline (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in Sertraline mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

CNS Active Drugs

In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either Sertraline (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the Sertraline group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the Sertraline group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of Sertraline did not significantly alter steady-state lithium levels or the renal clearance of lithium.

Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of Sertraline therapy with appropriate adjustments to the lithium dose.

In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozide AUC and Cmax of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of Sertraline and pimozide should be contraindicated.

Results of a placebo-controlled trial in normal volunteers suggest that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, at this time, it is recommended that plasma phenytoin concentrations be monitored following initiation of Sertraline therapy with appropriate adjustments to the phenytoin dose, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant medications.

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 following initiation of Sertraline therapy with appropriate adjustments to the valproate dose.

The risk of using Sertraline in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Sertraline and such drugs is required. There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual Dysphoric disorder and social anxiety disorder to Sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Monoamine Oxidase Inhibitors

Drugs Metabolized by P450 3A4

In three separate in vivo interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and Cmax were reduced by about 35%).

Drugs Metabolized by P450 2D6: Many drugs effective in the treatment of major depressive disorder, e.g., the SSRIs, including sertraline, and most tricyclic antidepressant drugs effective in the treatment of major depressive disorder inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase), and, thus, may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressant drugs effective in the treatment of major depressive disorder and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the drugs effective in the treatment of major depressive disorder in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with Sertraline may require lower doses than usually prescribed for the other drug. Furthermore, whenever Sertraline is withdrawn from co-therapy, an increased dose of the co-administered drug may be required.

Serotonergic Drugs

Triptans: There has been rare post marketing reports of serotonin syndrome with use of an SNRI or an SSRI and a triptans. If concomitant treatment of SNRIs and SSRIs, including SERTRALINE, with a triptans is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Sumatriptan: There has been rare post marketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and Sumatriptan. If concomitant treatment with Sumatriptan and an SSRI (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)

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

Hypoglycemic Drugs: In a placebo-controlled trial in normal volunteers, administration of Sertraline for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. Sertraline administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

Atenolol: SERTRALINE (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.

Digoxin: In a placebo-controlled trial in normal volunteers, administration of Sertraline for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.

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. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

Drugs That Interfere With Hemostasis (Non-selective NSAIDs, Aspirin, Warfarin, etc.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Sertraline is initiated or discontinued.

Electroconvulsive Therapy

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

Alcohol

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

ADVERSE EFFECTS:

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders–Frequent: impotence; Infrequent: flushing, increased saliva, cold clammy skin, mydriasis; Rare: pallor, angle-closure glaucoma, priapism, vasodilation.

Body as a Whole–General Disorders–Rare: allergic reaction, allergy.

Cardiovascular–Frequent: palpitations, chest pain; Infrequent: hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; Rare: precordial chest pain, sub sternal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders–Frequent: hypertonia, hypoesthesia; Infrequent: twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hyperkinesia; Rare: dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyperreflexia.

Disorders of Skin and Appendages–Infrequent: pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; Rare: follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders–Rare: exophthalmos, Gynecomastia.

Gastrointestinal Disorders–Frequent: appetite increased; Infrequent: dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; Rare: melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenses, colitis, diverticulitis, fecal incontinence, gastritis, rectum haemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.

General–Frequent: back pain, asthenia, malaise, weight increase; Infrequent: fever, rigors, generalized edema; Rare: face edema, aphthous stomatitis.

Hearing and Vestibular Disorders–Rare: hyperacusis, labyrinthine disorder.

Hematopoietic and Lymphatic–Rare: anaemia, anterior chamber eye haemorrhagee.

Liver and Biliary System Disorders–Rare: abnormal hepatic function.

Metabolic and Nutritional Disorders–Infrequent: thirst; Rare: hypoglycaemia, hypoglycaemia reaction.

Musculoskeletal System Disorders–Frequent: myalgia; Infrequent: arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.

Psychiatric Disorders–Frequent: yawning, other male sexual dysfunction, other female sexual dysfunction; Infrequent: depression, amnesia, paranoia, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; Rare: withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive–Infrequent: menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal haemorrhagee, amenorrhea, leucorrhoea; Rare: female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders–Frequent: rhinitis; Infrequent: coughing, Dyspnoea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; Rare: hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

Special Senses–Frequent: tinnitus; Infrequent: conjunctivitis, earache, eye pain, abnormal accommodation; Rare: exophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect.

Urinary System Disorders–Infrequent: micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; Rare: cystitis, oliguria, pyelonephritis, hematuria, and renal pain, stranger.

Other Events Observed during the Post marketing Evaluation of Sertraline

Reports of adverse events temporally associated with Sertraline that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including Torsade de Pointes arrhythmias), cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome), hypothyroidism, agranulocytosis, aplastic anaemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, diabetes mellitus, Hyperglycaemia, Galactorrhea, Hyperprolactinemia, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vacuities, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events—clinical features (which in the majority of cases appeared to be reversible with discontinuation of Sertraline) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

OVERDOSAGE AND TREATMENT:

Treatment should consist of those general measures employed in the management of over dosage with any antidepressant.

Ensure an 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 performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to large volume of distribution of this drug, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.

In managing over dosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

STORAGE CONDITION:

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:

Alu/PVC Blister Pack x 10's (Box of 30's and 100's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):

Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:

Marketing Authorization Holder

Brown & Burk Philippines Inc.
U-501, 5/F SEDCCO 1 Bldg., 120 Rada cor.
Legaspi Sts., Legaspi Village, Makati, Metro Manila

NAME AND ADDRESS OF MANUFACTURER:

MICRO LABS LIMITED

92 Sipcot Industrial Compex,
Hosur-635 126 (T.N), INDIA

CAUTION STATEMENT:

FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

ADR REPORTING STATEMENT:

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of Adverse Drug Reaction.

REGISTRATION NUMBER:

DR No. : XY34637

DATE OF FIRST AUTHORIZATION:

04 MAR, 2010.

DATE OF REVISION OF PACKAGE INSERT:

April 2018

EXG-ML01I-0092/F

MICRO LABS LIMITED, BANGALORE, INDIA			
1	Product Name	Zotral	Colours Used
2	Strength	50 mg	BLACK
3	Component	Leaflet	
4	Category	Export - Philippines	
5	Dimension	260 (L) x 360 (H) mm	
6	Artwork Code	EXG-ML01I-0092/F	
7	Pharma Code	773	
8	Reason for Change	Size, text and from 50 mg Film-coated Tablet to **50 mg Tablet** changed.	Colours not for Printing Keylines

	Prepared by (DTP)	Checked by (PD)	Approved by			
			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	Head QA (Site)
Sign	Kantharaju L.					
Date	14-09-2023					