SETROF TABLET

DESCRIPTION
Oblong, white to off white film-coated tablet, shallow convex with break bar on one side and HD embossed on the other side.

COMPOSITION
Sertraline Hydrochloride 56 mg equivalent to Sertraline 50 mg/tablet.

List of Excipients:
Hydroxypropyl Methylcellulose E-5, Hydroxypropyl Methylcellulose E-15, Dicalcium Phosphate Dihydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Magnesium Stearate, Colloidal Silicone Dioxide, Isopropyl Alcohol, Propylene Glycol, Talc, Titianium Dioxide and Purified water.

ACTIONS AND PHARMACOLOGY
Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake in vitro which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with downregulation of brain norepinephrine receptors as observed with other clinically effective antidepressants and antiobsessional drugs. No weight gain was observed in controlled clinical trials with sertraline treatment for depression or OCD; some patients may experience a reduction in body weight with sertraline. Sertraline has not demonstrated potential for abuse. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam.

PHARMACOKINECTICS
Sertraline exhibits dose proportional pharmacokinetics over the range of 50 to 200 mg. In man, following oral once daily dosing over the range of 50 to 200 mg for 14 days, peak plasma concentrations (Cmax) of sertraline occur at about 4.5 to 8.4 hours post dosing.
The pharmacokinetic profile in either adolescents or the elderly is not significantly different from that in adults between 18 and 65 years. The mean half-life of sertraline for young and elderly men and women ranges from 22 to 36 hours. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation up to steady state concentrations, which are achieved after 1 week of once daily dosing. Approximately 98% of the circulating drug is bound to plasma proteins.
Animal studies indicate that sertraline has a large apparent volume of distribution. Sertraline undergoes extensive first pass hepatic metabolism. The principal metabolite in plasma, N-desmethylsertraline, is substantially less active than sertraline (about 20 times) *in vitro* and there is no evidence of activity in *in vivo* models of depression. The half-life of N-desmethylsertraline is in the range of 62 to 104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in faeces and urine in equal amounts. Only a small amount (<0.2%) of unchanged sertraline is excreted in the urine.
Food does not significantly change the bioavailability of sertraline tablets.

INDICATIONS
Sertraline is indicated for the treatment of:
a) symptoms of depression, including depression accompanied by symptoms of anxiety, in patients with or without a history of mania. Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes.
b) obsessive compulsive disorder (OCD). Following initial response, sertraline has been associated with sustained efficacy, safety and tolerability in up to 2 years of treatment of OCD.
c) panic disorder, with or without agoraphobia.
d) post-traumatic stress disorder (PTSD).
e) social phobia (social anxiety disorder).
f) premenstrual dysphoric disorder (PMDD).

CONTRAINDICATIONS
- Contraindicated in patients with a known hypersensitivity to sertraline.
- Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.
- Concomitant use in patients taking pimozide is contraindicated.

WARNINGS AND PRECAUTIONS
Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS):
The development of potentially life-threatening syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) has been reported with SSRIs, including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of serotonergic drugs (including triptans and fentanyl), with drugs which impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. SS symptoms may include mental state 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). Some signs of SS, including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes resemble NMS. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome.
Monoamine Oxidase Inhibitors (MAOI):
Cases of serious reactions, sometimes fatal, have been reported in patients receiving sertraline in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI, selegiline and the reversible MAOI, moclobemide and MAOI drugs, e.g. linezolid. Some cases presented with features resembling the serotonin syndrome, the symptoms of which include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. Therefore, sertraline should not be used in combination with an MAOI or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should elapse after discontinuing sertraline treatment before starting an MAOI.
Other Serotonergic drugs:
Coadministration of sertraline with other drugs which enhance serotonergic neurotransmission, such as tryptophan or fenfluramine and fentanyl, 5-HT agonists, or the herbal medicine St. John's Wort (hypericum perforatum) should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction.
Switching from Selective Serotonin Reuptake Inhibitors (SSRIs), Antidepressants or Antiobsessional Drugs:
There is limited controlled experience regarding the optimal timing of switching from other antidepressants or antiobsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents such as fluoxetine. The duration of a washout period for switching from one SSRI to another has not been established.
Activation of Mania / Hypomania:
During premarketing testing, hypomania or mania occurred in approximately 0.4% of sertraline treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder treated with other marketed antidepressant and antiobsessional drugs.
Seizures:
Seizures are a potential risk with antidepressant and antiobsessional drugs. Since sertraline has not been evaluated in patients with a seizure disorder, it should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.
Suicide:
Since the possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs, patients should be closely supervised during the early course of therapy.
Abnormal Bleeding / Haemorrhage:
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) as well as in patients with a history of bleeding disorders.
Hyponatremia:
Hyponatremia may occur as a result of treatment with SSRIs or SNRIs including sertraline. In many cases, hyponatremia appears to be the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium levels lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also patients taking diuretics or who are otherwise volume-depleted may be at greater risk.

Discontinuation of sertraline should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest and death.
Because of the well-established comorbidity between OCD and depression, panic disorder and depression, and PTSD and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD, panic disorder or PTSD.
Use in Hepatic Insufficiency:
Sertraline is extensively metabolized by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and approximately three-fold greater AUC and Cmax in comparison to normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.
Use in Renal Insufficiency:
Sertraline is extensively metabolized. Excretion of unchanged drug in urine is a minor route of elimination. In studies of patients with mild to moderate renal impairment (creatinine clearance 30 - 60 ml/min) or moderate to severe renal impairment (creatinine clearance 10-29 ml/min), multiple dose pharmacokinetic parameters (AUC0-24 or Cmax) were not significantly different compared with controls. Half-lives were similar and there were no differences in plasma protein binding in all groups studied. As expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment.
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. Patients should therefore 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.
Laboratory Tests:
False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking sertraline. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of sertraline therapy. Confirmatory tests, such as gas chromatography or mass spectrometry, will distinguish sertraline from benzodiazepines.
Angle-Closure Glaucoma:
SSRIs including sertraline may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. Sertraline should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.
Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction.
There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

MAIN SIDE/ADVERSE EFFECTS
Side effects that occurred significantly more frequently with sertraline than with placebo in multiple-dose studies for depression were:
Autonomic Nervous System:
Dry mouth and increased sweating.
Central and Peripheral Nervous System:
Dizziness and tremor.
Gastrointestinal:
Diarrhea/loose stools, dyspepsia and nausea.
Psychiatric:
Anorexia, insomnia and somnolence.
Reproductive:
Sexual dysfunction (principally ejaculatory delay in males).

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

Voluntary reports of adverse events in patients receiving sertraline since market introduction have been received. They include the following:
Autonomic Nervous System:
Mydriasis and priapism.
Body as a Whole:
Allergic reaction, allergy, anaphylactoid reaction, asthenia, fatigue, fever, hot flushes, malaise, weight decrease and weight increase.

Cardiovascular:
Chest pain, edema peripheral, hypertension, palpitations, periorbital edema, syncope and tachycardia.
Central and Peripheral Nervous System:
Coma, convulsions, cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and call-fleming syndrome) headache, migraine, movement disorders (including extrapyramidal symptoms such as akathisia, dystonia, hyperkinesia, hypertonia, teeth grinding or gait abnormalities), muscle contractions involuntary, paresthesia and hypoesthesia. Also reported were signs and symptoms associated with serotonin syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhea, fever, hypertension, rigidity and tachycardia.
Endocrinological:
Galactorrhea, gynecomastia, hyperprolactinemia, hypothyroidism and syndrome of inappropriate ADH secretion (SIADH).
Gastrointestinal:
Abdominal pain, appetite increased, constipation, pancreatitis, vomiting and microscopic colitis.
Hearing/Vestibular: Tinnitus.
Hematopoietic:
Altered platelet function, abnormal bleeding (such as epistaxis, gastrointestinal bleeding or hematuria), leucopenia, purpura and thrombocytopenia.
Laboratory Changes:
Abnormal clinical laboratory results.
Liver/Biliary:
Serious liver events (including hepatitis, jaundice and liver failure) and asymptomatic elevations in serum transaminases (SGOT and SGPT).
Metabolic/Nutritional:
Hyponatremia and increased serum cholesterol, diabetes mellitus, hyperglycaemia and hypoglycaemia.
Musculoskeletal:
Arthralgia and muscle cramps.
Psychiatric:
Agitation, aggressive reaction, anxiety, depressive symptoms, euphoria, hallucination, libido decreased-female, libido decreased-male, paranoia, psychosis and yawning.
Reproductive: Menstrual irregularities.
Respiratory: Bronchospasm.
Skin:
Face edema, alopecia, angioedema, photosensitivity skin reaction, pruritus, rash (including rare reports of serious exfoliative skin disorders: e.g. Stevens-Johnson syndrome and epidermal necrolysis) and urticaria.
Renal and Urinary:
Enuresis, urinary incontinence and urinary retention.
Vision: Vision abnormal.
Other:
Symptoms following the discontinuation of sertraline have been reported and included agitation, anxiety, dizziness, headache, nausea and paresthesia.

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors:
See sections **Contraindications** and **Warnings** and **Precautions.**
Pimozide:
Concomitant administration of sertraline and pimozide is contraindicated.
CNS Depressants and Alcohol:
The concomitant use of sertraline and alcohol is not recommended.
Lithium:
In placebo-controlled trials in normal volunteers, the co-administration of sertraline with lithium did not significantly alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When co-administering sertraline with medications, such as lithium, which may act via serotonergic mechanisms, patients should be appropriately monitored.
Phenytoin:
It is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels.
Sumatriptan:
There have been rare post-marketing reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. If concomitant treatment with sertraline and sumatriptan is clinically warranted, appropriate observation of the patient is advised.
Other Serotonergic Drugs:
Concomitant administration of sertraline and Other Serotonergic Drugs should be undertaken with caution and avoided whenever possible.
Protein Bound Drugs:
Since sertraline is bound to plasma proteins, the potential of sertraline to interact with other plasma protein bound drugs should be borne in mind. However, in three formal interaction studies with diazepam, tolbutamide and warfarin respectively, sertraline was not shown to have significant effects on the protein binding of the substrate.
Warfarin:
Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.
Other Drug Interactions:
Co-administration of sertraline 200 mg daily with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters.
Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown.
Sertraline had no effect on the beta-adrenergic blocking ability of atenolol.
No interaction of sertraline 200 mg daily was observed with glibenclamide or digoxin.
Electroconvulsive Therapy (ECT):
There are no clinical studies establishing the risks or benefits of the combined use of ECT and sertraline.
Drugs Metabolized by Cytochrome P450 (CYP) 2D6:
There is variability among antidepressants in the extent to which they inhibit the activity of isozyme CYP2D6. The clinical significance of this depends on the extent of the inhibition and the therapeutic index of the co-administered drug. CYP 2D6 substrates with a narrow therapeutic index include TCAs and class 1C antiarrhythmics such as propafenone and flecainide. In formal interaction studies, chronic dosing with sertraline 50 mg daily showed minimal elevation (mean 23%-37%) of steady state desipramine plasma levels (a marker of CYP 2D6 isoenzyme activity).
Drugs Metabolized by Other CYP Enzymes (CYP 3A3/4, CYP 2C9, CYP 2C19, CYP 1A2):
The results of *in vivo* studies suggest that sertraline is not a clinically relevant inhibitor of CYP 3A/34, CYP 2C9, CYP 2C19. *In vitro* studies indicate that sertraline has little or no potential to inhibit CYP 1A2.

PREGNANCY AND LACTATION

Pregnancy:
Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 times and 10 times the maximum daily human mg/kg dose, respectively. There was no evidence of teratogenicity at any dose level. At the dose level corresponding to approximately 2.5 to 10 times the maximum daily human mg/kg dose, however, sertraline was associated with delayed ossification in fetuses, probably secondary to effects on the dams.
There was decreased neonatal survival following maternal administration of sertraline at doses approximately 5 times the maximum human mg/kg dose. Similar effects on neonatal survival have been described for other antidepressant drugs. The clinical significance of these effects is unknown.
There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sertraline should be used during pregnancy only if the perceived benefits outweigh the risks.
Lactation:
Limited data concerning sertraline levels in breast milk are available. Isolated studies in very small numbers of nursing mothers and their infants indicated negligible or undetectable levels of sertraline in infant serum, although levels in breast milk were more concentrated than in maternal serum. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefit outweighs the risk.
If sertraline is used during pregnancy and/or lactation, the physician should be aware that symptoms, including those compatible with withdrawal reactions, have been reported in some neonates whose mothers had been on SSRI antidepressants, including sertraline.
Women of childbearing potential should employ an adequate method of contraception if taking sertraline.
Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997 to 2005 found a PPHN risk ratio of 2.4 (95% CI 1.2 to 4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy".

SYMPTOMS AND TREATMENT FOR OVERDOSE

Deaths involving overdoses of sertraline, primarily in combination with other drugs and/or alcohol have been reported. Therefore, any overdosage should be treated aggressively. Symptoms of overdose include serotonin-mediated side effects such as somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness.
There are no specific antidotes to sertraline. Establish and maintain an airway, and ensure adequate oxygenation and ventilation, if necessary. Activated charcoal, which may be used with a cathartic, may be as or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.
Effects on Ability to Drive and Use Machines
Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However, as psychotropic drugs may impair the mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly.

DOSAGE AND ADMINISTRATION

Sertraline should be administered once daily, either in the morning or evening. Sertraline tablets can be administered with or without food.
Initial Treatment
Depression and OCD:
Sertraline treatment should be administered at a dose of 50 mg/day.
Panic Disorder, PTSD & Social Phobia:
Therapy should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.
Premenstrual Dysphoric Disorder:
Sertraline treatment should be initiated with a dose of 50mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.
Titration
Depression, OCD, Panic Disorder and PTSD:
Patients not responding to a 50 mg dose may benefit from dose increases. Dose changes should be made at intervals of at least one week, up to a maximum of 200 mg/day. Changes in dose should not be made more frequently than once per week given the 24 hour elimination half life of sertraline.
The onset of therapeutic effect may be seen within 7 days. However, longer periods are usually necessary to demonstrate therapeutic response, especially in OCD.
Premenstrual Dysphoric Disorder:
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.
Maintenance:
Dosage during long-term therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response.
Use in the Elderly:
The same dose range as in younger patients may be used in the elderly.
Use in Hepatic Insufficiency:
The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.
Use in Renal Insufficiency:
Sertraline is extensively metabolized. Excretion of unchanged drug in urine is a minor route of elimination. As expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store at or below 30°C.
Presentation/Packing: Blister pack of 3 x 10's and 10 x 10's.

Manufactured by: HOVID Bhd.
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