

SERALINE

Tablets

Composition

Seraline 50

Each tablet contains Sertraline 50 mg.

Action

Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake in vitro, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of brain norepinephrine receptors as observed with other clinically effective antidepressants and antiobsessional drugs.

Pharmacokinetics

Absorption

Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg. In man, following an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of sertraline occur at 4.5 to 8.4 hours after the daily administration of the drug. Food does not significantly change the bioavailability of sertraline tablets.

Distribution

Approximately 98% of the circulating drug is bound to plasma proteins.

Biotransformation

Sertraline undergoes extensive first-pass hepatic metabolism.

Based on clinical and in-vitro data, it can be concluded that sertraline is metabolized by multiple pathways including CYP3A4, CYP2C19 and CYP2B6. Sertraline and its major metabolite desmethylsertraline are also substrate of P-glycoprotein in-vitro.

Elimination

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

Indications

- Seraline is indicated for the treatment of symptoms of depression, including depression accompanied by symptoms of anxiety, in patients with or without a history of mania. Following satisfactory response, continuation with Seraline therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes.
- Seraline is indicated for the treatment of 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.
- Seraline is indicated for the treatment of paediatric patients with OCD.
- Seraline is indicated for the treatment of panic disorder, with or without agoraphobia.
- Seraline is indicated for the treatment of post-traumatic stress disorder (PTSD).

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

Contraindications

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

Adverse Reactions

Blood and Lymphatic System Disorders: Leucopenia and thrombocytopenia.

Cardiac Disorders: Palpitations and tachycardia.

Ear and Labyrinth Disorders: Tinnitus.

Endocrine Disorders: Hyperprolactinaemia, hypothyroidism and syndrome of inappropriate ADH secretion (SIADH).

Eye Disorders: Mydriasis and vision abnormal.

Gastrointestinal Disorders: abdominal pain, constipation, pancreatitis and vomiting.

General Disorders and Administration Site Conditions: Asthenia, chest pain, oedema peripheral, fatigue, fever and malaise.

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

Immune System Disorders: Allergic reactions, allergy and anaphylactoid reaction.

Investigations: Abnormal clinical laboratory results, altered platelet function, increased serum cholesterol, weight decrease and weight increase.

Metabolism and Nutrition Disorders: Appetite increased and hyponatremia

Musculoskeletal and Connective Tissue Disorders: Arthralgia and muscle cramps.

Nervous System Disorders: Coma, convulsions, headache, migraine, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, teeth grinding or gait abnormalities), muscle contractions involuntary, paraesthesia hypoesthesia and syncope. Also reported were signs and symptoms associated with serotonin syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia.

Psychiatric Disorders: Agitation, aggressive reaction, anxiety, depressive symptoms, euphoria, hallucination, libido decreased-female, libido decreased-male, paranoia and psychosis.

Renal and Urinary Disorders: Urinary incontinence and urinary retention.

Reproductive System and Breast Disorders: Galactorrhoea, gynecomastia, menstrual irregularities and priapism.

Respiratory, Thoracic and Mediastinal Disorders: Bronchospasm and yawning.

Skin and Subcutaneous Tissue Disorders: Alopecia, angioedema, face oedema, periorbital oedema, photosensitivity skin reaction, pruritus, rash (including rare reports of serious exfoliative skin disorders: e.g. Stevens-Johnson syndrome and epidermal necrolysis) and urticaria.

Vascular Disorders: Hot flushes and hypertension. Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, hematomas, vaginal bleeding and gastrointestinal bleeding.

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

Warnings and Precautions

Activation of mania/hypomania

Hypomania or mania may occur in patients treated with sertraline. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants and antiobsessional agents.

Weight loss

Significant weight loss may be an undesirable result of treatment with sertraline for some patients, approximately 0.5 kg – 1.0 kg weight loss.

Seizure

Seizures have been observed occasionally in patients using sertraline. Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for sertraline should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Weak uricosuric effect

Sertraline is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Electroconvulsive therapy

There are no clinical studies establishing the risks or benefits of combined use of ECT and sertraline.

Driving/Use of machinery

Sertraline has no effect on psychomotor performance. However patients should be cautioned accordingly when driving a car or operating machinery.

Use in patients with concomitant illness

Caution is advisable in using sertraline in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Sertraline has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease.

Liver impairment

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. The elimination half-life of sertraline is prolonged. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver disease, a lower or less frequent dose should be considered.

Renal impairment

In patients with mild to moderate renal impairment (creatinine clearance 20–60 mL/min) or severe renal impairment (creatinine clearance <30 mL/min) multiple dose pharmacokinetic parameters (AUC or C_{max}) are modest, sertraline should be used with care in these patients. The dose of sertraline may have to be reduced in patients with impaired renal function.

Interference with cognitive and motor performance

Sertraline does not cause sedation and does not interfere with psychomotor performance.

Safety and efficacy in children under 18 years of age have not been established.

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behavior has not been established. Patients being treated with sertraline should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania, and mania. Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing sertraline, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, sertraline should be tapered.

Use in pregnancy

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Use in 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.

Children

Safety and effectiveness in paediatric patients below the age of 6 have not been established. Sertraline should not be used in children and adolescents below the age of 18 years for the treatment of major depressive disorder. The efficacy and safety of sertraline has not been satisfactorily established for the treatment of major depressive disorder in this age group.

Geriatric Use

The pattern of adverse reactions in the elderly was similar to that in younger patients.

Drug Interactions

Monoamine Oxidase Inhibitors

Cases of serious reactions, sometimes fatal, have been reported in patients receiving sertraline in combination with a MAOI, including the selective MAOI, selegiline, and the reversible MAOI, moclobemide.

Some cases presented with features resembling neuroleptic malignant syndrome. Similar cases, sometimes fatal, have been reported with other antidepressants during combined treatment with a MAOI and in patients who have recently discontinued an antidepressant or antiobsessional drug and have been started on a MAOI. Symptoms of a drug interaction between a 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.

Therefore, 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 elapse after discontinuing sertraline treatment and starting a MAOI.

Pimozide

Increased pimozide levels have been demonstrated in a study of single low dose pimozide (2 mg) with sertraline coadministration. These increased levels were not associated with any changes in EKG. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated.

CNS Depressants and Alcohol

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

Lithium

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

Chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, it is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels.

Sumatriptan

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

Other Serotonergic Drugs

Co-administration of sertraline with other agents which enhance serotonergic neurotransmission, such as tryptophan or fenfluramine, should be avoided due to the potential for pharmacodynamic interaction.

St John's Wort

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

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.

Medicines that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc)

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 medicines concurrently with sertraline.

Cimetidine

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

CNS active drugs

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

Hypoglycemic drugs

Co-administration of sertraline 200 mg daily with tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters. The clinical significance of these changes is unknown. Sertraline 200 mg daily did not affect the pharmacokinetics of glibenclamide. Patients receiving biguanides should monitor their blood glucose carefully when sertraline is introduced.

Atenolol

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

Digoxin

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

Electroconvulsive Therapy (ECT)

There are no clinical studies establishing the risks or benefits of the combined use of ECT and sertraline.

Drugs Metabolised by Cytochrome P450 (CYP) 2D6

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

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

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

CYP 2C9 - The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of tolbutamide, phenytoin and warfarin suggests that sertraline is not a clinically relevant inhibitor of CYP 2C9.

CYP 2C19 - The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of diazepam suggests that sertraline is not a clinically relevant inhibitor of CYP 2C19.

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

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.

Dosage and Administration

SERALINE should be administered once daily, either in the morning or evening. SERALINE 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 and Social Phobia

Therapy for panic disorder, PTSD and social phobia should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.

Premenstrual Dysphoric Disorder

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

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

Titration

For all indications other than PMDD

Patients not responding to a 50 mg dose may benefit from dose increases. Dose changes should be made at intervals of at least one week, up to a maximum of 200 mg/day (refer to section above for details on dosage titration for PMDD).

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

Maintenance

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

Use in Children

The safety and efficacy of sertraline has been established in paediatric OCD patients aged 6 to 17. The administration of sertraline to paediatric OCD patients (aged 13 to 17) should commence at 50 mg/day.

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

Titration in Children and Adolescents

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

Use in the Elderly

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

Use in Hepatic Insufficiency

The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.

Use in Renal Insufficiency

Sertraline is extensively metabolised. Excretion of unchanged drug in urine is a minor route of elimination. As expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Over Dosage

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

There are no specific antidotes to sertraline. Establish and maintain an airway and ensure adequate oxygenation and ventilation, if necessary. Activated charcoal, which may be used with a cathartic, may be as or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended. Cardiac and vital sign monitoring is recommended along with general symptomatic and supportive measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

Pharmaceutical Precautions

Store below 30°C

Presentation

Seraline 50

Box of 30 tablets