

LUSTRAL

TABLETS

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Composition

Each tablet contains:

Active Ingredient

Sertraline (as hydrochloride) 50 mg or 100 mg

Other Ingredients

Microcrystalline cellulose, calcium hydrogen phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polysorbates, titanium dioxide.

Mechanism of 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, gamma-aminobutyric acid (GABA) or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with downregulation of norepinephrine receptors as observed with other clinically effective antidepressant drugs.

Unlike tricyclic antidepressants, no weight gain is observed with treatment for depression; some patients may experience a reduction in body weight with sertraline.

In humans and animal studies, sertraline has not demonstrated potential for abuse. In a placebo-controlled, double blind, randomized study of the comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria and abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforcer in rhesus monkeys trained to self-administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

Pharmacokinetics

Sertraline exhibits dose proportional pharmacokinetics over the range of 50 to 200 mg. In man, following oral once daily dosing over the range of 50 to 200 mg for 14 days, peak plasma concentrations (C_{max}) of sertraline occur at about 4.5 to 8.4 hours post dosing. The pharmacokinetic profile in either adolescents or the elderly is not significantly different from that in adults between 18 and 65 years. The mean half-life of sertraline for young and elderly men and women ranges from 22-36 hours.

Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation up to steady state concentrations, which are achieved after 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 62-104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in feces 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

Lustral is indicated for the treatment of symptoms of depression 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.

Contraindications

Patients with a known hypersensitivity to sertraline, or to any other ingredient of the preparation.

Concomitant use in patients taking monoamine oxidase (MAO) inhibitors (see Warnings).

Warnings

(See Contraindications and Drug Interactions)

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

Coadministration of sertraline with other drugs which enhance the effects of serotonergic neurotransmission, such as tryptophan or fenfluramine or 5-HT agonists, 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 SSRIs, antidepressants or antiobsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents such as fluoxetine. The duration of washout period which should intervene before switching from one SSRI to another has not been established.

Preclinical Data

Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective.

Mutagenicity

Sertraline has also been shown to be devoid of mutagenic effects.

Use in Pregnancy and Lactation

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

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.

Use in Pediatrics

The safety and effectiveness of sertraline in children have not been fully established.

In clinical trials in patients aged 6-17 years with depression, sertraline appeared to have a similar pharmacokinetic profile to that found in adults.

Use 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 Patients with Impairment of Hepatic Function

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 C_{max} in comparison to normal subjects.

There were no significant differences in plasma protein binding observed between the two groups. The use of sertraline in patients with hepatic disease should be approached

with caution. A lower or less frequent dose should be used in patients with hepatic impairment.

Use in Patients with Impairment of Renal Function

Sertraline is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 30-60 ml/min) or moderate to severe renal impairment (creatinine clearance 10-29 ml/min), multiple dose pharmacokinetic parameters (AUC₀₋₂₄ or C_{max}) were not significantly different compared with controls. Half-lives were similar and there were no differences in plasma protein binding in all groups studied. This study indicates that, as expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment.

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, or in patients with diabetes or peptic ulcer.

Adverse Reactions

Clinical Trial Data:

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).

Post-Marketing Data: 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, headache, migraine, movement disorders (including extrapyramidal symptoms such as 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.

Gastrointestinal: Abdominal pain, appetite increased, constipation, pancreatitis and vomiting.

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.

Musculoskeletal: Arthralgia.

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

Reproductive: Menstrual irregularities.

Respiratory: Bronchospasm.

Skin: 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.

Urinary: Face edema, 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.

Precautions

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 drugs.

Seizures

Seizures are a potential risk with antidepressant drugs. Seizures were reported in approximately 0.08% of patients treated with sertraline in the development program for depression. In all these cases, the relationship to sertraline therapy was uncertain. Since sertraline has not been evaluated in patients with a seizure disorder, it should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

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.

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. As with any CNS active drug, the physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of sertraline misuse or abuse (e.g development of tolerance, incrementation of dose, drug-seeking behavior).

Drug Interactions

Sertraline/Monoamine Oxidase Inhibitors: See Contraindications and Warnings.

Sertraline/Other Serotonergic Drugs: See Warnings.

Sertraline/Alcohol/CNS Depressants: 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.

Sertraline/Phenytoin: A placebo-controlled trial in normal volunteers suggests that chronic administration of sertraline 200mg/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.

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

Sertraline/Other Plasma 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 3 formal interaction studies with diazepam, tolbutamide, and warfarin respectively, sertraline was not shown to have significant effects on the protein binding of the substrate (see subsections *Warfarin and Sertraline/Diazepam/Tolbutamide/Cimetidine/ Glibenclamide/Atenolol/Digoxin*).

Sertraline/Diazepam/Tolbutamide/Cimetidine/Glibenclamide/Atenolol/Digoxin: Formal drug interaction studies have been performed with sertraline. 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 β -adrenergic blocking ability of atenolol. No interaction of sertraline 200mg daily was observed with glibenclamide or digoxin.

Sertraline/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.

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

Sertraline/Drugs Metabolized by Other CYP Enzymes:

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

CYP 2C9: The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of tolbutamide, phenytoin and warfarin suggests that sertraline is not a clinically relevant inhibitor of CYP 2C9 (see subsections *Warfarin*, *Phenytoin* and *Sertraline/Diazepam/Tolbutamide/Cimetidine/Glibenclamide/Atenolol/Digoxin*).

CYP 2C19: The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of diazepam suggests that sertraline is not a clinically relevant inhibitor of CYP 2C19 (see subsection *Sertraline/Diazepam/Tolbutamide/Cimetidine/Glibenclamide/Atenolol/Digoxin*).

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

Sertraline/Lithium: In placebo-controlled trials in normal volunteers, the combined administration of lithium and sertraline did not alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When coadministering sertraline with medications, such as lithium, which may act via serotonergic mechanisms, patients should be appropriately monitored.

Therapeutic Interference

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

Dosage and Administration

Lustral should be administered once daily, either in the morning or evening. Lustral tablets can be administered with or without food. The usual therapeutic dose is

50 mg/day. This dose may be increased in case of lack of response in 50 mg/day increments to a maximum of 200 mg/day over a period of weeks. The onset of therapeutic effect may be seen within 7 days; however, for full antidepressant activity, 2-4 weeks are usually necessary. All changes should not occur at intervals at less than one week.

Dosage during prolonged maintenance therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response. Lustral, as with many other medications, should be used with caution in patients with renal and hepatic impairment (see Warnings).

There are insufficient data regarding any benefits from treatment beyond 16 weeks.

Use in the Elderly

The same dose range as in younger patients may be used in the elderly.

Overdosage

Manifestations

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

Treatment

No specific therapy is recommended and 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.

Presentation

28 tablets.

Manufacturer

Pfizer Inc. Sandwich, England

DRUGS-ABOUT.COM

For

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