LUSTRAL

TABLETS

Composition

Each tablet contains:

Active Ingredient

Sertraline (as hydrochloride) 50 mg or 100 mg

Other Ingredients

Microcrystalline cellulose, calcium hydrogen phosphate dihydrate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, purified water, white opadry, clear opadry

Mechanism of Action

Sertraline is a potent and selective inhibitor of neuronal serotonin (5-HT) reuptake *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 down regulation of norepinephrine receptors as observed with other clinically effective antidepressant drugs.

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 (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 22-36 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).

Concomitant use in patients taking pimozide is contraindicated (see Drug Interactions).

Warnings

(See Contraindications and Drug Interactions)

Monoamine Oxidase Inhibitors

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, the reversible MAO inhibitor, moclobemide and MAO inhibitor drugs, e.g., linezolid . 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.

Other Serotonergic Drugs

Co-administration of sertraline with other drugs which enhance the effects of serotonergic neurotransmission, such as tryptophan, or fenfluramine, or 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.

Serotonin syndrome

Caution is advisable if Lustral is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan.

In rare cases, serotonin syndrome has been reported in patients using SSRIs/ SNRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI/ SNRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

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.

In one epidemiological study, the use of SSRIs after the first 20 weeks of pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The absolute risk among those who used SSRIs late in pregnancy was reported to be about 6 to 12 per 1000 women, compared to 1 to 2 per 1000 women in the general population

Another epidemiologic study suggests that exposure to these drugs in the first trimester of pregnancy may be associated with an increased risk of cardiac birth defects.

A study in pregnant women who were treated with selective serotonin reuptake inhibitors (SSRIs), illustrated the potential risk of relapsed depression after stopping antidepressant medication during pregnancy. In this study, women who stopped their medicine were five times more likely to have a relapse of depression during their

pregnancy than were women who continued to take their antidepressant medicine while pregnant. Women who are pregnant or thinking about becoming pregnant should not stop this antidepressant medication without first consulting their physician.

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 of post-marketing reports of symptoms, including those compatible with withdrawal reactions, 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 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 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 (AUC_{0-24} 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. 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.

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. No seizures were reported in patients treated with sertraline in the development program for panic. During the development program for OCD, four out of approximately 1,800 patients exposed to sertraline experienced seizures (approximately 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. 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.

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.(see section Drug Interaction).

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 (see Use in Elderly). 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, PTSD and depression, and social phobia and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD, panic disorder, PTSD or social phobia.

Adverse Reactions

Clinical Trial Data:

Side effects that occurred significantly more frequently with sertraline than with placebo in multiple-dose studies for depression were:

Gastrointestinal Disorders: Diarrhea/loose stools, dry mouth, dyspepsia and nausea.

Metabolism and Nutrition Disorders: Anorexia.

Nervous System Disorders: Dizziness, somnolence and tremor.

Psychiatric Disorders: Insomnia.

Reproductive system and Breast Disorders: Sexual dysfunction (principally ejaculatory delay in males).

Skin and Subcutaneous Tissues Disorders: Increased sweating.

Post-Marketing Data

Voluntary reports of adverse events in patients receiving sertraline since market introduction have been received. They include the following:

Blood and Lymphatic System Disorders: Leucopenia and thrombocytopenia.

Cardiac Disorders: palpitations and tachycardia.

Ear and Labyrinth Disorders: Tinnitus.

Endocrin Disorders: Hyperprolactinemia, hypothyroidism and syndrome of inappropriate ADH secretion.

Eye Disorders: Mydriasis and vision abnormal.

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

General Disorders and Administration Site Conditions: Asthenia, chest pain, edema 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 reaction, 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 increase and Hyponatremia.

Musculoskeletal and Connective Tissue Disorders: Arthralgia and muscle cramps.

Nervous System Disorders: Coma, convulsions, headache, hypoesthesia, migraine, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, teeth grinding or gait abnormalities), muscle contractions involuntary, paresthesia 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, diarrhea, fever, hypertension, rigidity and tachycardia.

Psychiatric Disorders:,Aggressive reaction, agitation, anxiety, depressive symptoms, euphoria, hallucination, libido decreased-female, libido decreased-male, paroniria and psychosis.

Renal and Urinary Disorders: Enuresis, urinary incontinence and urinary retention.

Reproductive System and Breast Disorders: Galactorrhea, gynecomastia, Menstrual irregularities and priapism.

Respiratory, Thoracic and Mediastinal Disorders: Bronchospasm and yawning.

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

Vascular Disorders: Abnormal bleeding (such as epistaxis, gastrointestinal bleeding or hematuria), hot flushes and hypertention.

Other: Symptoms following the discontinuation of sertraline have been reported and included agitation, anxiety, dizziness, headache, nausea and paresthesia.

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

serltraline 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/Pimozide: Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) with sertraline co-administration. 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.

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. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels.

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 dose not inhibit the CYP 3A3/4 mediated metabolism of alprazolam. The data 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.

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For

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