PRESCRIBING INFORMATION

(For the use of a registered medical practitioner or a hospital or a laboratory.)

SERTIMA-50 MG TABLETS
(Sertraline Hydrochloride Tablets 50 mg)

COMPOSITION

Each film coated tablet contains
Sertraline Hydrochloride Ph. Eur. equivalent
to Sertraline.....50 mg

DESCRIPTION

White to off-white, biconvex with beveled edge capsule shape film coated tablets with inscription 'I' and 'C' on either side of break line on one side and plain on the other side.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (alpha1, $alpha_2$, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_1A$, $5HT_1B$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics:

Systemic Bioavailability–In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range.

Metabolism–Sertraline undergoes extensive first pass metabolism. The principal initial pathway

of metabolism for sertraline is N-demethylation. N- desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N- desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation.

Protein Binding–Sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol.

Liver Disease–As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10).

INDICATIONS

Sertraline 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 sertraline therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes.

Sertraline is indicated for the treatment of obsessive-compulsive disorder (OCD).

Sertraline is indicated for the treatment of panic disorder, with or without agoraphobia.

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 disorders:
Therapy for panic disorder 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 frequency of early treatment emergent side effects characteristics of panic disorder.

Titration
Depression, OCD and Panic Disorder:
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.
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 effectiveness of sertraline in children have not been fully established.

Use in 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 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.

Route of Administration:

Sertima-50 is tablet for oral use.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. Concomitant use in patients taking pimozide is contraindicated. Sertraline hydrochloride is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients in Sertima-50.

WARNINGS

Suicidality in children and adolescents

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescent with major depressive disorder (MDD) and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- Sertima-50 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 be allowed after stopping Sertima-50 before starting an MAOI.

PRECAUTIONS

General

Activation of Mania/Hypomania–Hypomania or mania occurred in approximately 0.4% of sertraline treated patients.

Weight Loss–Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.

Seizure– Sertraline has not been evaluated in patients with a seizure disorder. No seizures were observed among approximately 3000 patients treated with sertraline in the development program for major depressive disorder.

Discontinuation of Treatment with Sertima-50

During marketing of sertraline and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania.

Patients should be monitored for these symptoms when discontinuing treatment with Sertima-50. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake.

Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SERTIMA-50 with non-selective NSAIDs (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2), aspirin, or other drugs that affect coagulation.

Weak Uricosuric Effect–SERTIMA-50 (sertraline hydrochloride) is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Use in Patients with Concomitant Illness– Caution is advisable in using SERTIMA-50 in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Hyponatremia– Several cases of hyponatremia have been reported and appeared to be reversible when sertraline was discontinued.

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

DRUG INTERACTIONS

Potential Effects of Co-administration of Drugs Highly Bound to Plasma Proteins– Because sertraline is tightly bound to plasma protein, the administration of SERTIMA-50 (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect.

Conversely, adverse effects may result from displacement of protein bound SERTIMA-50 by other tightly bound drugs.

CNS Active Drugs– The risk of using SERTIMA-50 in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of SERTIMA-50 and such drugs is required.

Drugs Metabolized by P450 3A4–In three separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance.

Drugs Metabolized by P450 2D6– Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition.

Consequently, concomitant use of a drug metabolized by P450 2D6 with SERTIMA-50 may require lower doses than usually prescribed for the other drug. Furthermore, whenever SERTIMA-50 is withdrawn from co-therapy, an increased dose of the co-administered drug may be required.

Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)– Nevertheless, caution is indicated in the co- administration of TCAs with SERTIMA-50 , because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored and the dose of TCA may need to be reduced, if a TCA is co-administered with SERTIMA-50.

Drugs That Interfere With Hemostasis (Non-selective NSAIDs, Aspirin, Warfarin, etc.)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between the use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper

gastrointestinal bleeding have also shown that concurrent use of a non-selective NSAID (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2) or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with SERTIMA-50.

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

Labor and Delivery–The effect of Sertima-50 on labor and delivery in humans is unknown.

Nursing Mothers–It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sertima-50 is administered to a nursing woman.

PREGNANCY

Sertima is administered during pregnancy only if potential benefits outweigh the risk to the foetus. It is excreted into the breast milk hence it should not be used during lactation. Safety and efficacy has not been established in children. Observational data indicate an increased risk (less than 2 fold) of postpartum haemorrhage following SSRI/NSRI exposure within the month prior to birth.

ADVERSE REACTIONS

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

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

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

Cardiovascular–*Frequent:* palpitations, chest pain;
Infrequent: hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema;

Rare: precordial chest pain, sub-sternal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

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

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

Endocrine Disorders–*Rare:* exophthalmos, gynecomastia.

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

General–*Frequent:* back pain, asthenia, malaise, weight increase;

Infrequent: fever, rigors, generalized edema; *Rare:* face edema, aphthous stomatitis.

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

Hematopoietic and Lymphatic–*Rare:* anemia, anteriorchamber eye hemorrhage.

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

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

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

Psychiatric Disorders–*Frequent:* yawning, other male sexual dysfunction, other female sexual dysfunction;

Infrequent: depression, amnesia, paroniria, teeth- grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions;

Rare: withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive–*Infrequent:* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea;

Rare: female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders–*Frequent:* rhinitis;
Infrequent: coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis;

Rare: hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

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

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

OVERDOSAGE

Human Experience–
The most common signs and symptoms associated with non-fatal sertraline hydrochloride over dosage were somnolence, vomiting, tachycardia, nausea, dizziness, agitation and tremor. The largest known ingestion was 13.5 grams in a patient who took sertraline hydrochloride alone and subsequently recovered. However, another patient who took 2.5 grams of sertraline hydrochloride alone experienced a fatal outcome.

Other important adverse events reported with sertraline hydrochloride overdose (single or multiple drugs) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor and syncope.

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

Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

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

In managing over dosage, consider the possibility of multiple drug involvement.

PACK SIZE
Sertima –50 mg tablets is available in PVC-Alu. blister pack with pack size of 2 x 14 tablets.

STORAGE
Store below 30 °C.
Keep out of the reach and sight of children.

SHELF LIFE
2 years

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