APPROVED PROFESSIONAL INFORMATION (Clean)

SCHEDULING STATUS

S5

PROPRIETARY NAME (and dosage form)

AUROLIFT 50 mg (Tablet)

AUROLIFT 100 mg (Tablet)

COMPOSITION

AUROLIFT 50 mg: Each film-coated tablet contains Sertraline Hydrochloride equivalent to Sertraline 50 mg.

AUROLIFT 100 mg: Each film-coated tablet contains Sertraline Hydrochloride equivalent to Sertraline 100 mg.

PHARMACOLOGICAL CLASSIFICATION

A 1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION

Sertraline is a potent and selective inhibitor of neuronal sertonin (5-HT) uptake. It has only weak effects on neuronal uptake of norepinephrine and dopamine.

Sertraline does not enhance catecholaminergic activity and it has no affinity for cholinergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), dopaminergic, adrenergic ($alpha_1$, $alpha_2$, beta) histaminergic, GABA or benzodiazepine receptors.

In a single-dose study, sertraline exhibited dose proportional pharmacokinetics over the range 50 mg-200 mg. After oral administration over the range of 50 to 200 mg once daily for 14 days, mean peak blood levels were reached at 4,5-8,4 hours post dose. The average terminal plasma half-life is about 26 hours. Steady-state plasma levels are reached after approximately one week of once daily dosing. Approximately

98% of the circulating drug is bound to plasma proteins. Consistent with the terminal elimination half-life, there is approximately two-fold accumulation with repeated dosing as compared to a single dose. Sertraline undergoes extensive first pass hepatic metabolism. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown the principal metabolite, N-desmethylsertraline, to have significantly less clinical activity. Both sertraline and N-desmethylsertraline are extensively metabolised with only a small amount (<0,2%) of unchanged sertraline excreted in the urine. About 40-45% of the dose administered radioactively was recovered in the urine and a similar amount in the faeces, including 12-14% unchanged sertraline. The terminal elimination half-life of N-desmethylsertraline is approximately 62 to 104 hours. Desmethylsertraline exhibits time related dose dependent increases in AUC, Cmax and Cmin with a 5 to 9 fold increase in their parameters between day 1 and day 14.

Protein binding - In vitro protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL.

Age - Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 year old) individuals. Steady state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.

Liver disease - The administration of sertraline is delayed in patients with impaired liver function. Dosages should be reduced. (See Warnings)

INDICATIONS:

AUROLIFT is indicated for the treatment of major depressive disorders such as single episodes and recurrent depression.

AUROLIFT is also indicated for the treatment of obsessive compulsive disorder (OCD). AUROLIFT is also indicated for the treatment of panic disorder, with or without agoraphobia.

Panic disorder:

Panic disorder is characterised by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and /or a

significant change in behaviour related to the attacks. Panic disorder is characterised by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, light-headed, or faint; (9) derealisation (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of loosing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes. The physician who elects to use AUROLIFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Dosage and Directions for Use).

CONTRA-INDICATIONS

AUROLIFT is contra-indicated in patients with known hypersensitivity to sertraline. The concomitant use of AUROLIFT with a monoamine oxidase inhibitor (MAOI) is contra-indicated -see "Warnings".

Use in hepatic or renal insufficiency - see "Warnings - Use in patients with concomitant illness".

WARNINGS

Activation of mania/hypomania - Activation of mania/hypomania may occur in 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.

Seizure- AUROLIFT should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. AUROLIFT 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 AUROLIFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Electroconvulsive therapy - There are no clinical studies establishing the risks or benefits of combined use of ECT and AUROLIFT.

Driving/Use of machinery - Clinical pharmacology studies have shown that 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 AUROLIFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

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

Renal impairment - AUROLIFT should be used with care in these patients. The dose of AUROLIFT may have to be reduced in patients with impaired renal function.

INTERACTIONS

Monoamine oxidase inhibitors - Cases of serious reactions, sometimes fatal, have been reported in patients receiving AUROLIFT in combination with a MAOI, including the selective MAOI, selegiline, and the reversible MAOI, moclobemide. Some cases presented with features resembling neuroleptic malignant syndrome. 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, AUROLIFT 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.

CNS depressants and alcohol - The concomitant use of AUROLIFT and alcohol in depressed patients is not recommended.

Protein bound medicines - *In vitro* protein binding studies performed with radiolabeled ^{3}H-sertraline showed that 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 medicines, viz. warfarin and propranolol. 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. (see also Other Interactions).

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

Switching from other antidepressants or antiobsessional agents - There is limited controlled experience regarding the optimal timing of switching from other antidepressants or antiobsessional agents to AUROLIFT. Care and prudent medical judgement 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 selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Other interactions - Co-administration of AUROLIFT (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.

Warfarin - Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time. Accordingly prothrombin time should be carefully monitored when AUROLIFT therapy is initiated or stopped.

No interactions reported with the following:

AUROLIFT has no effect on the beta-adrenergic blocking ability of atenolol. No interaction of sertraline 200 mg daily was observed with glibenclamide or digoxin.

Lithium - In placebo-controlled trials in normal volunteers, the combined administration of lithium and AUROLIFT did not alter lithium pharmacokinetics. It is recommended that plasma lithium levels be

monitored following initiation of AUROLIFT therapy, so that appropriate adjustments to the lithium dose may be made if necessary. Co-administration with lithium may lead to a higher incidence of 5HT-associated side effects, resulting in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. Therefore, caution is recommended when co-administering sertraline with medications such as lithium, which may act via serotonergic mechanisms.

Medicines metabolised by cytochrome P450 (CYP) 2D6 - There is variability among antidepressants in the extent of clinically important inhibition of the drug metabolising isoenzyme CYP 2D6 and, in formal interaction studies, chronic dosing with sertraline 50 mg daily showed minimal elevation of steady state desipramine plasma levels (a marker of CYP 2D6 isoenzyme activity)

Medicines metabolised by other CYP enzymes - *In vivo* interaction studies have demonstrated that chronic administration of AUROLIFT 200 mg daily does not inhibit the CYP 3A3/4 mediated 6-beta hydroxylation of endogenous cortisol or the metabolism of carbamazepine or terfenadine.

The apparent lack of clinically significant effects of the chronic administration of AUROLIFT 200 mg daily on plasma concentrations of tolbutamide, phenytoin and warfarin suggests that AUROLIFT is not a clinically relevant inhibitor of CYP 2C9. The apparent lack of clinically significant effects of the chronic administration of AUROLIFT 200 mg daily on plasma concentrations of diazepam suggests that AUROLIFT is not a clinically relevant inhibitor of CYP 2C19. *In vitro* studies indicate that AUROLIFT has little or no potential to inhibit CYP 1A2.

PREGNANCY AND LACTATION

Safety during pregnancy and lactation has not been established. AUROLIFT should be used in pregnancy and during lactation only if the perceived benefits outweigh the risks. Women of child-bearing potential should employ an adequate method of contraception if taking AUROLIFT.

DOSAGE AND DIRECTIONS FOR USE

AUROLIFT tablets should be given as a single daily dose with or without food.

Depression

The starting dose is 50 mg daily and the usual therapeutic dose in depression is 50 mg daily. In difficult to treat patients, the dose may be titrated up in 50 mg increments at 2 weekly intervals, to 150 mg-200 mg.

Obsessive-Compulsive Disorder

The minimum effective dose in OCD is also 50 mg daily and increases above 100 mg daily does not have any additional benefit. Full activity is usually seen after 2-4 weeks and even longer in OCD. Effect may however be seen within 7 days.

Panic Disorder

For panic disorder, the minimum recommended effective dose of sertraline is 50 mg/day. However, therapy for panic disorder should commence at 25 mg/day, increasing to 50 mg/day after one week. This dosage regimen has been demonstrated to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.

Use in the elderly - No special precautions are required. The usual adult dosage is recommended.

Use in children - The use of AUROLIFT in children is not recommended as safety and efficacy have not been established.

Use in hepatic and renal impairment - see “Warnings - Use in patients with concomitant illness”.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side Effects:

Gastrointestinal disorders:

Common: Constipation, diarrhoea, nausea, vomiting, dyspepsia, flatulence, anorexia, abdominal pain, appetite increased, dry mouth, taste perversion.

Nervous system disorders:

Common: Headache, paresthesia, hypoesthesia, twitching, hypertonia, tremor; dizziness, insomnia, somnolence, convulsions.

Cardiac disorders: Palpitations

Skin and subcutaneous tissue disorders: Rash, erythema multiforme.

General disorders: Fatigue, increased sweating, hot flushes, fever, back pain.

Metabolism and nutrition disorders: Thirst.

Musculoskeletal, connective tissue and bone disorders: Myalgia arthralgia, movement disorders (such as gait abnormalities).

Psychiatric disorders: Agitation, nervousness, anxiety, yawning, impaired concentration, psychosis, depressive symptoms, hallucinations, aggressive reaction, agitation.

Renal and urinary disorders: Micturition frequency, micturition disorder, urinary retention.

Hepato-biliary disorders: Pancreatitis and serious liver events (including hepatitis, jaundice and liver failure).

Reproductive system and breast disorders: Menstrual Symptoms, female sexual dysfunction, sexual dysfunction (primarily ejaculatory delay in males).

Respiratory, thoracic and mediastinal disorders: Rhinitis, pharyngitis.

Eye disorders: Vision abnormal.

Ear and labyrinth disorders: Tinnitus.

Investigations:

Asymptomatic elevations of serum transaminases (SGOT and SGPT) have been reported infrequently (approximately 0,8%) in association with AUROLIFT therapy. There have been rare reports of altered platelet function and/or abnormal clinical laboratory results in patients taking AUROLIFT.

Hyponatraemia, possibly due to inappropriate antidiuretic hormone secretion, has been associated with the use of antidepressants, particularly in the elderly.

Special precautions:

There have been reports of extrapyramidal symptoms associated with the use of AUROLIFT and of aggravation of Parkinson's disease in patients taking AUROLIFT. Caution should be exercised when prescribing AUROLIFT to patients with extrapyramidal disorders and patients should be carefully monitored.

Abrupt discontinuation of AUROLIFT may lead to withdrawal symptoms which include dizziness, sweating, nausea, insomnia, tremor, confusion, sensory disturbances, agitation and anxiety.

AUROLIFT should be used with caution in patients with hepatic or renal impairment; reduced doses should be considered in patients with hepatic impairment.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Serious sequelae have not been reported following overdoses of sertraline alone of up to 6 g. Although there have been no deaths reported when sertraline was taken alone, deaths involving overdoses of sertraline in combination with other medicines and/or alcohol have been reported. Therefore, any overdosage should be treated aggressively.

No specific therapy is recommended and there are no specific antidotes to sertraline. Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, a cathartic, may be as, or more, effective than emesis or lavage, and should be considered in treating overdosage. Monitoring of cardiac and vital signs 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.

IDENTIFICATION

AUROLIFT 50 mg- White coloured, biconvex, capsule shaped film coated tablets debossed with 'A' on one side and with a score line in between '8' and '1' on the other side.

AUROLIFT 100 mg**-** White coloured, biconvex, capsule shaped film coated tablets debossed with 'A' on one side and '82' on the other side.

PRESENTATION

Two types of blister packaging material:

1. Tablets are packed in Clear PVC (250 microns) as the forming material and aluminium foil (25 microns) as the lidding material. Each blister contains 10 tablets.
2. Tablets are packed in Clear PVC (250 microns) coated with PVdC (60gsm) as the forming material and aluminium foil (25 microns) as the lidding material. Each blister contains 10 tablets.

AUROLIFT 50 mg: 30's (3 x 10's)

AUROLIFT 100 mg: 30's (3 x 10's)

STORAGE INSTRUCTIONS

Store below 25°C.

Keep out of reach of children.

REGISTRATION NUMBER

AUROLIFT 50 mg: A40/1.2/0654

AUROLIFT 100 mg: A40/1.2/0655

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