PI FOR SERDEP 100 TABLETS

SCHEDULING STATUS

S5

PROPRIETARY NAME (STRENGTH AND DOSAGE FORM)

SERDEP 100 (Tablets)

COMPOSITION

Each SERDEP 100 tablet contains 112 mg sertraline hydrochloride equivalent to 100 mg sertraline.

Other inactive ingredients include:

Core Tablet:

Calcium hydrogen phosphate dihydrate, magnesium stearate, maize starch, microcrystalline cellulose and sodium starch glycolate.

Film Coating:

Ferric oxide (yellow), hypromellose (methocel E50LV premium), propylene glycol, purified talc and Titanium dioxide.Sugar Free

PHARMACOLOGICAL CLASSIFICATION

A 1.2 Psychoanaleptics (Antidepressants).

PHARMACOLOGICAL ACTION

Pharmacodynamics

Sertraline presumably acts by inhibiting neuronal uptake of serotonin (5HT) in the central nervous system. In human platelets, sertraline inhibits serotonin uptake. Sertraline is a serotonin-specific neuronal re-uptake inhibitor with weak inhibition of noradrenaline (norepinephrine) and dopamine neuronal uptake. In animals, sertraline does not act as a stimulant or a sedative, has no anticholinergic activity and is not cardiotoxic. Sertraline has no catecholaminergic effects and does not bind to serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), adrenergic ($alpha_1$, $alpha_2$, beta), histaminergic, cholinergic, dopaminergic, GABA or benzodiazepine receptors.

In animals, down-regulation of brain noradrenaline receptors was associated with chronic sertraline administration. This is an observation typical of other clinical effective antidepressants.

Pharmacokinetics

Over the range of 50 to 200 mg, sertraline exhibits dose-dependent pharmacokinetics. With a once daily dose of 50 to 200 mg for 14 days, mean peak blood concentrations are reached 4,5 to 8,4 hours after dose administration. Sertraline has an average terminal plasma half-life of approximately 26 hours. A once daily dose results in steady-state plasma levels after approximately one week. Sertraline is highly protein bound (approximately 98 % binds to plasma proteins). Compared to a single dose, repeated dosing results in an approximate two-fold accumulation of sertraline.

Sertraline is extensively metabolised on first pass in the liver. The principal metabolite, N-desmethylsertraline has significantly less clinical activity than sertraline

according to *in vitro* biochemical and *in vivo* pharmacological testing. Both sertraline and N-desmethylsertraline undergoes extensive metabolism with less than 0,2 % unchanged sertraline excreted in the urine. When a radioactive dose was administered, 40 to 45 % of the dose was recovered in the urine and the same amount in the faeces. Of this, 12 to 14 % was unchanged sertraline. N-desmethylsertraline has a terminal half-life of 62 to 104 hours. The increases in AUC, C_{max} and C_{min} of desmethylsertraline are time-related and dose-dependent. A 5- to 9-fold increase in these parameters is observed between day 1 and 14 after dose administration.

Protein binding:

At 20 to 500 ng/ml, sertraline is 98 % serum protein bound.

Age:

The elderly have a 40 % lower plasma clearance of sertraline compared to younger (25 to 32 years) individuals. Therefore, steady state should be achieved after 2 to 3 weeks in older patients. A decreased clearance of desmethylsertraline is observed in older men, but not in older women.

Liver disease:

Dosages of sertraline should be reduced in patients with impaired liver function due to delayed metabolism of sertraline (see **"WARNINGS"**).

INDICATIONS

SERDEP 100 is indicated for the treatment of:

- major depressive disorders, such as single episodes and recurrent depression.
- obsessive-compulsive disorder (OCD).
- panic disorder, with or without agoraphobia.

Panic disorder

Patients with panic disorders characteristically suffer unexpected panic attacks. Such patients are also concerned about having additional attacks, worry about the implications and consequences of these attacks and/or significant behavioural changes resulting from the attacks.

Recurrent, unexpected panic attacks are characteristic of panic disorder. During a panic attack the patient experiences a discrete period of intense fear or discomfort in which four or more of the following symptoms develop suddenly and reach peak intensity within ten minutes: sweating; trembling or shaking; palpitations, pounding heart, or accelerated heart rate; chest pain or discomfort; sensations of shortness of breath or smothering; feeling of choking; nausea or abdominal distress; feeling dizzy, unsteady, light-headed, or faint; paraesthesiae (numbness or tingling sensations); chills or hot flushes; derealisation (feelings of unreality) or depersonalisation (being detached from oneself); fear of losing control; and fear of dying.

The long-term effectiveness (when used for more than 12 weeks) of SERDEP 100 has not been evaluated. Therefore, physicians treating patients for extended periods with SERDEP 100 should, for each treated patient, re-evaluate the long-term usefulness of the medicine periodically (see **"DOSAGE AND DIRECTIONS FOR**

USE").

CONTRA-INDICATIONS

SERDEP 100 is contra-indicated in:

- patients with known hypersensitivity to sertraline.
- patients concomitantly using a monoamine oxidase inhibitor (MAOI) (see **"WARNINGS"**).
- children under the age of 18 years (see **"WARNINGS"** and **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**).
- hepatic or renal insufficiency (see **"WARNINGS - Use in patients with concomitant illness"**).

WARNINGS

Activation of mania/hypomania

SERDEP 100 may cause hypomania or mania. Other marketed antidepressants and anti-obsessional agents have also been implicated in the activation of mania/hypomania in a small proportion of patients with major affective disorder.

Weight loss

A significant weight loss of approximately 0,5 kg to 1,0 kg may be expected in some patients on SERDEP 100.

Seizures

Occasional seizures have been reported in patients using SERDEP 100. Patients with unstable epilepsy should avoid using SERDEP 100 and patients with controlled

epilepsy should be carefully monitored. Discontinue SERDEP 100 in any patient who develops seizures.

Weak uricosuric effect

SERDEP 100 decreases serum uric acid by approximately 7 %. It is not known if this weak uricosuric effect is clinically significant.

Electroconvulsive therapy (ECT)

The risks or benefits of the concomitant use of ECT and SERDEP 100 have not been clinically established.

Use in patients with concomitant illness

Care should be taken in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Myocardial infarction or unstable heart disease

SERDEP 100 has not been evaluated or used to a great extent in these patients.

Liver impairment

The primary site of metabolism of SERDEP 100 is the liver. Hence, liver impairment prolongs the elimination half-life of SERDEP 100. SERDEP 100 must be used cautiously in patients with liver disease. If SERDEP 100 is administered to patients with liver disease, the dose must be lowered, or the frequency of dosing should be reduced.

Renal impairment

Mild to moderate renal impairment (creatinine clearance 30 to 60 ml/min) or severe renal impairment (creatinine clearance < 30 ml/min), modestly affects multiple dose pharmacokinetic parameters (AUC or C_{max}). Use SERDEP 100 with care in these patients. The dose of SERDEP 100 may have to be reduced.

Interference with cognitive and motor performance

SERDEP 100 has no sedative or psychomotor effects.

Children

Safety and efficacy in children under 18 years of age have not been established (see **"CONTRA-INDICATIONS"** and **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**).

Suicide

Patients (both adults and children) with major depressive disorder may feel more depressed and/or experience episodes of suicidal ideation and behaviour, independent of taking antidepressants. Until significant remission occurs, this remains a risk. A cause-and-effect relationship between antidepressants and such behaviour has not been established. Patients taking SERDEP 100 should, nevertheless, be closely monitored for clinical worsening and suicidality, especially at the start of therapy or when a change in dosage, either up or down is made. Prescriptions for SERDEP 100 should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders is possible. Therefore, patients treated for major depressive disorders and patients treated for other psychiatric and non-psychiatric disorders should be observed with the same precautions.

Patients being treated with antidepressants for major depressive disorder or for other psychiatric or non-psychiatric disorders may present with the following symptoms: panic attacks, anxiety, agitation, insomnia, irritability, impulsivity, akathisia, hostility (aggressiveness), hypomania, and mania. There is no link between the emergence of suicidal impulses and SERDEP 100. However, in patients where suicidal impulses are severe, abrupt in onset, or were not part of their presenting symptoms, the SERDEP 100 treatment regimen should be changed, or possibly discontinued.

In the event of discontinuation of SERDEP 100 treatment, the dose should be tapered (see **"DOSAGE AND DIRECTIONS FOR USE"** and **"Special Precautions"**).

Abnormal bleeding/Haemorrhage

There have been reports of bleeding abnormalities with SSRIs including cutaneous bleeding (ecchymoses and purpura) and other haemorrhagic events such as gastrointestinal or gynaecological bleeding, including fatal haemorrhages. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see **'PREGNANCY AND LACTATION'** and **'SIDE-EFFECTS AND SPECIAL PRECAUTIONS'**). Caution is advised in patients taking SSRIs, particularly in concomitant use with medicines

known to affect platelet function (e.g. anticoagulants, atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs) as well as in patients with a history of bleeding disorders (see **'INTERACTIONS'**).

INTERACTIONS

Monoamine oxidase inhibitors

Reports of serious reactions, sometimes fatal, in patients receiving SERDEP 100 in combination with a MAOI, including the selective MAOI, selegiline, and the reversible MAOI, moclobemide, have been made. Features resembling neuroleptic malignant syndrome have been reported. Similar cases, some of them fatal, have been reported with the concomitant use of other antidepressants and a MAOI as well as cases of patients who have recently discontinued an antidepressant or anti-obsessional medicine and have been started on a MAOI. Interactions between a SSRI and a MAOI present with the following symptoms: rigidity, myoclonus, hyperthermia, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma.

SERDEP 100 should therefore not be used concomitantly with a MAOI or within 2 weeks of discontinuing MAOI treatment. Similarly, at least 2 weeks should elapse between starting treatment with a MAOI and SERDEP 100 discontinuation.

CNS depressants and alcohol

Depressed patients should not use SERDEP 100 concomitantly with alcohol.

Special precautionary monitoring is advised with the following

Protein bound medicines:

In the range of 20 to 500 ng/ml, SERDEP 100 is 98 % serum protein bound.

However, SERDEP 100 at up to 300 and 200 ng/ml respectively, does not alter the plasma protein binding of either warfarin or propranolol. SERDEP 100 also has no significant effects on the protein binding of diazepam or tolbutamide (see also **"Other interactions"**).

Serotonergic agents:

Due to the potential for pharmacodynamic interaction, co-administration of SERDEP 100 and other agents which enhance serotonergic neurotransmission, such as tryptophan or fenfluramine, is not advisable.

Switching from other antidepressants or anti-obsessional agents:

There is limited data regarding the optimal time to switch from other antidepressants or anti-obsessional agents to SERDEP 100. When switching, particularly from long-acting agents such as fluoxetine, special care and discreet medical judgement should be exercised. There is no clear indication as to the duration of a washout period between cessation of one selective serotonin reuptake inhibitor (SSRI) and starting another.

Other interactions

Diazepam, as well as tolbutamide, results in small, but statistically significant changes in some pharmacokinetic parameters of SERDEP 100, when co-administered.

SERDEP 100 clearance is substantially decreased when co-administered with cimetidine. The clinical significance of this is unknown.

Warfarin

A small but statistically significant increase in prothrombin time is observed during sertraline 200 mg daily and warfarin co-administration. In the event of initiation or cessation of SERDEP 100 therapy, prothrombin time should be carefully monitored.

Lithium

Plasma lithium levels should be monitored following initiation of SERDEP 100 therapy. Appropriate adjustments to the lithium dose may be necessary. The incidence of 5HT-associated side-effects may increase during lithium co-administration, resulting in an increase in tremor compared to placebo, which is indicative of a pharmacodynamic interaction. Therefore, care should be taken during the co-administration of SERDEP 100 and lithium or other medicines with serotonergic effects.

Medicines affecting platelet function

The risk of bleeding may be increased when medicines acting on platelet function (e.g. NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might increase bleeding risk are concomitantly administered with SSRIs, including

sertraline (see **'WARNINGS'**).

No interactions reported with the following:

SERDEP 100 does not alter the beta-adrenergic blocking effects of atenolol. SERDEP 100, in a dose of 200 mg daily, does not interact with glibenclamide or digoxin.

Medicines metabolised by cytochrome P450 (CYP) 2D6

The extent of clinically important inhibition of CYP 2D6 by antidepressants varies. Chronic dosing with sertraline, as in SERDEP 100, 50 mg daily, shows minimal elevation of the steady state plasma levels of desipramine (a marker of CYP 2D6 isoenzyme activity).

Medicines metabolised by other CYP enzymes

Chronic administration of SERDEP 100, 200 mg daily, does not inhibit the 6-β-hydroxylation of endogenous cortisol by CYP 3A3/4, nor does it inhibit carbamazepine or terfenadine metabolism.

Chronic administration of SERDEP 100, 200 mg daily, has no clinically significant effects on the plasma concentrations of tolbutamide, phenytoin and warfarin. This suggests that SERDEP 100 is not a clinically relevant inhibitor of CYP 2C9. Likewise, chronic administration of SERDEP 100, 200 mg daily, has no clinically significant effect on the plasma concentrations of diazepam. This suggests that SERDEP 100 is not a clinically relevant inhibitor of CYP 2C19. SERDEP 100 also has little or no potential to inhibit CYP 1A2.

PREGNANCY AND LACTATION

The safety of SERDEP 100 in pregnancy and breast feeding is not known. Women of child-bearing age should use adequate methods of contraception when using SERDEP 100.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see **'WARNINGS'** and **'SIDE-EFFECTS AND SPECIAL PRECAUTIONS'**).

DOSAGE AND DIRECTIONS FOR USE

SERDEP 100 should be administered as a single daily dose. It can be taken with or without food.

Depression

The starting dose in patients with depression is 50 mg daily and the usual therapeutic dose in depression is 50 mg daily. In difficult-to-treat patients, dose increases in 50 mg increments at 2-weekly intervals, to a maximum of 150 to 200 mg, is recommended.

Obsessive-compulsive disorder (OCD)

The minimum effective dose is 50 mg daily. Increases above 100 mg daily do not have additional benefit.

Full activity is observed after 2 to 4 weeks, or longer in OCD.

Effect may, however, be observed within 1 week.

Panic disorder

The starting dose is 25 mg (of an appropriate formulation) daily, increasing to 50 mg daily after one week.

The minimum recommended effective dose is 50 mg daily.

This dosage regimen reduces the frequency of early treatment emergent side-effects.

Use in the elderly:

Adult dose is recommended. No special precautions required.

Use in children:

The safety and efficacy of SERDEP 100 in children have not been established. Its use is not recommended.

Use in hepatic and renal impairment:

See **"WARNINGS - Use in patients with concomitant illness"**.

Discontinuation of therapy:

Discontinuation of SERDEP 100 therapy to the dose of SERDEP 100 should be tapered (see **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-Effects

Endocrine disorders

Less frequent:	Hyperprolactinaemia, galactorrhoea.

Metabolic and nutrition disorders

Frequent:	Increased sweating, dry mouth.
Less frequent:	Thirst.

Psychiatric disorders

Frequent:	Sexual dysfunction (primarily ejaculatory delay in males), insomnia, and somnolence.
Less frequent:	Agitation, nervousness, anxiety, psychosis, and female sexual dysfunction.

The following side-effects have been reported and frequencies are unknown:

In children reports of hostility, suicidal ideation and self-harm.

Nervous system disorders

Frequent:	Tremor, dizziness.
Less frequent:	Headache, paraesthesia, hypoesthesia, twitching, hypertonia, movement disorders (such as gait abnormalities), yawning, impaired concentration, convulsions, and taste perversion.

The following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: paraesthesia, hypoesthesia, depressive symptoms, hallucinations, aggressive reaction, agitation, anxiety and

psychosis.

Eye disorders

Less frequent:	Abnormal vision.

Ear and labyrinth disorders

Less frequent:	Tinnitus.

Cardiac disorders

Less frequent:	Palpitations.

Respiratory, thoracic and mediastinal disorders

Less frequent:	Rhinitis, pharyngitis.

Gastrointestinal disorders

Frequent:	Anorexia, nausea, diarrhoea/loose stools and dyspepsia.
Less frequent:	Constipation, vomiting, flatulence, abdominal pain and appetite increase.
	Pancreatitis.

Hepatobiliary disorders

Less frequent:	Serious liver events (including hepatitis, jaundice and liver failure).

Skin and subcutaneous tissue disorders

Less frequent: Rash, erythema multiforme.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Myalgia.

Renal and urinary disorders

Less frequent: Micturition frequency, micturition disorder.

Reproductive system and breast disorders

Less frequent: Menstrual symptoms.

Frequency unknown: Postpartum haemorrhage*.

*This event has been reported for the therapeutic class of SSRIs/SNRIs (see **'WARNINGS'** and **'PREGNANY AND LACTATION'**).

General disorders

Less frequent: Fatigue, hot flushes, fever, back pain.

Other

To avoid withdrawal symptoms such as dizziness, sweating, nausea, insomnia, tremor, confusion, sensory disturbances, agitation and anxiety, the dose of SERDEP 100 should be tapered when discontinuation of treatment is indicated (see **"DOSAGE AND DIRECTIONS FOR USE"** and **"Special Precautions"**).

Special Precautions

Parkinson's disease

Extrapyramidal symptoms and aggravation of Parkinson's disease in patients taking SERDEP 100 have been reported. Care should be taken when prescribing SERDEP 100 to patients with extrapyramidal disorders. Patients should be carefully monitored.

Discontinuation

Sudden discontinuation of SERDEP 100 administration can result in withdrawal effects. These include irritability, agitation, dysphoric mood, dizziness, anxiety, confusion, headache, lethargy, emotional lability, sensory disturbances (e.g. paraesthesiae), insomnia, and hypomania. Although these events are in general self-limiting, serious withdrawal symptoms have been reported.

All patients in which discontinuation of SERDEP 100 treatment is indicated should be carefully monitored for withdrawal symptoms. Tapering of the dose is recommended. Should intolerable symptoms occur in response to a decreased dose, the previously effective dose should be resumed. Thereafter, the physician may continue tapering the dose, but at a slower rate (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Laboratory abnormalities

Serum transaminases (AST and ALT)

SERDEP 100 therapy is associated with asymptomatic elevations of AST and ALT (infrequently – approximately 0,8 %). This normally occurs within the first 1 to 9 weeks of treatment and promptly stops upon discontinuation of SERDEP 100.

Platelet function

SERDEP 100 therapy is associated with altered platelet function and/or abnormal clinical laboratory results. There have been reports of abnormal bleeding or purpura in several patients taking SERDEP 100, but it is unclear whether SERDEP 100 has a causative role.

Hyponatraemia

SERDEP 100 therapy is associated with hyponatraemia. The effects appeared to be reversible when SERDEP 100 was discontinued. It is possible that some reported cases were due to inappropriate antidiuretic hormone secretion. Most of the reports were associated with the elderly and patients taking diuretics or other medications.

Children

Hostility, suicidal ideation and self-harm have been reported in children on SERDEP 100 therapy.

The safety and efficacy of SERDEP 100 in children younger than 18 years have not been established. Clinical trials on major depressive disorder revealed increased incidence of hostility and suicide-related adverse events, such as suicidal ideation and self-harm in children (see **"CONTRA-INDICATIONS"**).

Driving/Use of machinery

SERDEP 100 has no psychomotor effects. Caution should, however, be taken when driving a car or operating a machine.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS

TREATMENT

Available evidence suggests that SERDEP 100 has a wide margin of safety when used in overdose. No serious events have been reported following overdoses of sertraline of up to 6 g. Although SERDEP 100 in overdose cannot be linked to any deaths, overdoses of SERDEP 100 in combination with other medicines and/or alcohol have been associated with deaths. Any overdosage should be treated aggressively.

There is no specific therapy for overdosage and there are no specific antidotes to SERDEP 100.

An open airway, adequate oxygenation and ventilation should be maintained. Activated charcoal, with or without added sorbitol or a cathartic, may be just as effective as emesis or lavage; this should be considered in treating overdosage. Cardiac and vital signs should be monitored, along with general symptomatic and supportive treatment. SERDEP 100 has a large volume of distribution, hence forced diuresis, dialysis, haemoperfusion, and exchange transfusion will have no benefit.

IDENTIFICATION

Yellow coloured, round, biconvex, film coated tablets with a score line on one side and plain on the other side.

PRESENTATION

Blister strips of 10 tablets packed in 30’s in a carton.

STORAGE INSTRUCTIONS

Store in a dry place at or below 25 °C. Protect from light. Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

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