# PROFESSIONAL INFORMATION FOR SERDEP 50

# TABLETS

## SCHEDULING STATUS

S5

## PROPRIETARY NAME (AND DOSAGE FORM)

**SERDEP 50** Tablets

## COMPOSITION

Each **SERDEP 50** tablet contains sertraline hydrochloride equivalent to 50 mg sertraline.

The other ingredients are magnesium stearate, maize starch, microcrystalline cellulose, purified talc, sodium starch glycollate.
Flexicoat Protect Blue V6 (coating material) contains blue no 2 lake, carmoisine lake (E122), kollicoat protect, talc and titanium dioxide (E171).

## PHARMACOLOGICAL CLASSIFICATION

A 1.2 Psychoanaleptics (Antidepressants).

## PHARMACOLOGICAL ACTION

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 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 norepinephrine receptors was associated with chronic sertraline administration. This is an observation typical of other clinical effective antidepressants.

**Pharmacokinetics**

Over the range of 50 – 200 mg, sertraline exhibits dose-dependent pharmacokinetics. With a once daily dose of 50 - 200 mg for 14 days, mean peak blood concentrations are reached 4,5 – 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 % of unchanged sertraline excreted in the urine. When a radioactive dose was administered, 40 – 45 % of the dose was recovered in the urine and the same amount in the faeces. Of this, 12 – 14 % was unchanged sertraline. N-desmethylsertraline has a terminal half-life of 62 – 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 - 500 ng/mL, sertraline is 98 % serum protein bound.

**Age:**

The elderly has a 40 % lower plasma clearance of sertraline compared to younger (25 - 32 years) individuals. Therefore, steady state should be achieved after 2 - 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 50** 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; paraesthesias (numbness or tingling sensations); chills or hot flushes; derealisation (feelings of unreality) or depersonalisation (being detached from oneself); fear of losing control; fear of dying.

The long-term effectiveness (when used for more than 12 weeks) of **SERDEP 50** has not been evaluated. Therefore, physicians treating patients for

extended periods with **SERDEP 50** should, for each treated patient, re-evaluate the long-term usefulness of the medicine periodically (see **“DOSAGE AND DIRECTIONS FOR USE”**).

**CONTRAINDICATIONS**

**SERDEP 50** is contraindicated 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 50** 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 – 1,0 kg may be expected in some patients on **SERDEP 50**.

**Seizures:** - Occasional seizures have been reported in patients using **SERDEP 50**. Patients with unstable epilepsy should avoid using **SERDEP 50**

and patients with controlled epilepsy should be carefully monitored. Discontinue **SERDEP 50** in any patient who develops seizures.

**Suicide: -** Suicide attempts are inherent in depression and may persist until significant remission occurs. High-risk patients should be closely monitored during initial drug therapy. To reduce the risk of overdose, **SERDEP 50** should be prescribed in the smallest quantity of tablets consistent with good patient management.

**Weak uricosuric effect** - **SERDEP 50** decreases serum uric acid by approximately 7 %. It is not known if this weak uricosuric effect is clinically significant.

**Electroconvulsive therapy** – The risks or benefits of the concomitant use of ECT and **SERDEP 50** has not been clinically established.

**Driving/Use of machinery** - **SERDEP 50** has no psychomotor effects. Caution should however be taken when driving a car or operating a machine.

**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 50** has not been evaluated or used to a great extent in these patients.

**Liver impairment** – The primary site of metabolism of **SERDEP 50** is the liver. Hence, liver impairment prolongs the elimination half-life of **SERDEP 50**. **SERDEP 50** must be used cautiously in patients with liver disease. If **SERDEP 50** 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 20 - 60 mL/min) or severe renal impairment (creatinine clearance < 30 mL/min), modestly affects multiple dose pharmacokinetic parameters (AUC or $C_{max}$). Use **SERDEP 50** with care in these patients. The dose of **SERDEP 50** may have to be reduced.

**Interference with cognitive and motor performance** - **SERDEP 50** has no sedative or psychomotor effects.

**Children under 18 years of age** – Safety has not been established (see **"CONTRAINDICATIONS"** and **"SIDE EFFECTS AND SPECIAL PRECAUTIONS"**).

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 50** 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.

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 disorder 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 50**. However, in patients where suicidal impulses are severe, abrupt in onset, or were not part of their presenting symptoms, the **SERDEP 50** treatment regimen should be changed, or possibly discontinued.

In the event of discontinuation of **SERDEP 50** treatment, the dose should be tapered (see **“Special Precautions”** and **“DOSAGE AND DIRECTIONS FOR USE"**).

Selective-serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) may increase the risk of postpartum haemorrhage (see **“PREGNANCY AND LACTATION” and “SIDE EFFECTS”).**

**INTERACTIONS**

**Monoamine oxidase inhibitors** – Reports of serious reactions, sometimes fatal, in patients receiving **SERDEP 50** 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. Drug 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 50** 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 50** discontinuation.

**CNS depressants and alcohol** - Depressed patients should not use **SERDEP 50** concomitantly with alcohol.

***Special precautionary monitoring is advised with the following:***

**Protein bound medicines** – In the range of 20 – 500 ng/mL, **SERDEP 50** is 98 % serum protein bound.

However, **SERDEP 50** at up to 300 and 200 ng/mL respectively, does not alter the plasma protein binding of either warfarin or propranolol. **SERDEP 50** also has no significant effects on the protein binding of diazepam or tolbutamide and respectively (see also **"Other Interactions"**).

**Serotonergic agents** - Due to the potential for pharmacodynamic interaction, co-administration of **SERDEP 50** 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 50**. 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 result in small, but statistically significant changes in some pharmacokinetic parameters of **SERDEP 50**, when co-administered.

**SERDEP 50** 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 **SERDEP 50**, 200 mg daily and warfarin co-administration. In the event of initiation or cessation of **SERDEP 50** therapy, prothrombin time should be carefully monitored.

***No interactions reported with the following:***

**SERDEP 50** does not alter the beta-adrenergic blocking effects of atenolol.

**SERDEP 50**, 200 mg daily, does not interact with glibenclamide or digoxin.

**Lithium** – Plasma lithium levels should be monitored following initiation of **SERDEP 50** 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 50** and lithium or other medicines with serotonergic effects.

**Medicines metabolised by cytochrome P450 (CYP) 2D6** - The extent of clinically important inhibition of CYP 2D6 by antidepressants varies. Chronic dosing with **SERDEP 50,** 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 50,** 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 50,** 200 mg daily, has no clinically significant effects on the plasma concentrations of tolbutamide, phenytoin and warfarin. This suggests that **SERDEP 50** is not a clinically relevant inhibitor of CYP 2C9. Likewise, chronic administration of **SERDEP 50**, 200 mg daily, has no clinically significant effect on the plasma concentrations of diazepam. This suggests that **SERDEP 50** is not a clinically relevant inhibitor of CYP 2C19. **SERDEP 50** also has little or no potential to inhibit CYP 1A2.

## PREGNANCY AND LACTATION

The safety of **SERDEP 50** in pregnancy and breastfeeding is not known. Women of child-bearing age should use adequate methods of contraception when using **SERDEP 50**.

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**”).

## DOSAGE AND DIRECTIONS FOR USE

**SERDEP 50** should be administered as a single daily dose. It can be taken with or without food.

**Depression:**

Usual therapeutic dose: 50 mg daily.

Starting dose: 50 mg daily.

In difficult to treat patients, dose increases in 50 mg increments at 2 weekly intervals, to a maximum of 150-200 mg, is recommended.

**Obsessive-Compulsive Disorder:**

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

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

Effect may however be observed within 1 week.

**Panic Disorder:**

Starting dose: 25 mg daily, increasing to 50 mg daily after one week.

Minimum recommended effective dose: 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 50** in children have not been established. The use is not recommended.

**Use in hepatic and renal impairment** - see **("WARNINGS - Use in patients with concomitant illness")**.

Discontinuation of **SERDEP 50** therapy – the dose of **SERDEP 50** should be tapered (see **"Special Precautions"** and **"DOSAGE AND DIRECTIONS FOR USE"**).

**SIDE EFFECTS AND SPECIAL PRECAUTIONS**

**Side effects:**

**SERDEP 50** is associated with the following common adverse events:

Gastrointestinal complaints such as anorexia, nausea, diarrhoea/loose stools and dyspepsia; tremor; dizziness; insomnia; somnolence; increased sweating; dry mouth; and sexual dysfunction (primarily, ejaculatory delay in males).

**The following adverse events were also observed**:

*Cardiovascular disorders*:

Palpitations - frequency is unknown.

*Central and peripheral nervous system disorders*:

Headache, paraesthesia, hypoaesthesia, twitching, hypertonia - frequency is unknown.

*Disorders of skin and appendages*:

Rash - frequency is unknown.

*Gastrointestinal disorders*:

Constipation, vomiting, flatulence, anorexia, abdominal pain and increased appetite - frequency is unknown.

*General disorders*:

Fatigue, hot flushes, fever and back pain - frequency is unknown.

*Metabolic and nutritional disorders*:

Thirst - frequency is unknown.

*Musculoskeletal disorders*:

Myalgia - frequency is unknown.

*Psychiatric disorders*:

Agitation, nervousness, anxiety, yawning, female sexual dysfunction, impaired concentration and psychosis - frequency is unknown.

*Reproductive disorders*:

Menstrual symptoms - frequency is unknown.

Frequency not known: Postpartum haemorrhage*

**This event has been reported for the therapeutical class of SSRIs/SNRIs (see "**WARNINGS**" and "**PREGNANCY AND LACTATION**").*

*Respiratory disorders*:

Rhinitis and pharyngitis - frequency is unknown.

*Special senses disorders:*

Abnormal vision, tinnitus and taste perversion - frequency is unknown.

*Urinary disorders*:

Micturition frequency and micturition disorder - frequency is unknown.

Extrapyramidal symptoms and aggravation of Parkinson's disease in patients taking **SERDEP 50** have been reported. Care should be taken when prescribing **SERDEP 50** to patients with extrapyramidal disorders. Patients should be carefully monitored.

To avoid withdrawal symptoms such as dizziness, sweating, nausea, insomnia, tremor, confusion, sensory disturbances, agitation and anxiety, the dose of **SERDEP 50** should be tapered when discontinuation of treatment is indicated.

***Other side effects include*:** convulsions, movement disorders (such as gait abnormalities), hyperprolactinaemia, galactorrhoea and rarely, erythema, multiforme, pancreatitis and serious liver events (including hepatitis, jaundice and liver failure). Other adverse events which have been rarely reported include: paraesthesia, hypoaesthesia, depressive symptoms, hallucinations, aggressive reaction, agitation, anxiety and psychosis. These events can

however not be distinguished from the natural history of the underlying disease.

**Laboratory abnormalities:**

**Serum transaminases (SGOT and SGPT)**: - **SERDEP 50** therapy is associated with asymptomatic elevations of SGOT and SGPT (infrequently - approximately 0,8 %). This normally occurs within the first 1 to 9 weeks of treatment and promptly stops upon drug discontinuation.

**Platelet function**: - **SERDEP 50** 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 50,** but it is unclear whether **SERDEP 50** has a causative role.

**Hyponatraemia:** - **SERDEP 50** therapy is associated with hyponatraemia. The effects appeared to be reversible when **SERDEP 50** 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.

**Hostility, suicidal ideation and self-harm:** – This has been reported in children on **SERDEP 50** therapy.

The safety and efficacy of **SERDEP 50** 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 **“CONTRAINDICATIONS”**).

Sudden discontinuation of **SERDEP 50** administration can result in withdrawal effects. These include: irritability, agitation, dysphoric mood, dizziness, anxiety, confusion, headache, lethargy, emotional lability, sensory disturbances (e.g. paraesthesias), insomnia, and hypomania. Although these events are in general self-limiting, serious withdrawal symptoms have been reported.
All patients in which discontinuation of **SERDEP 50** 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"**).

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

Available evidence suggests that **SERDEP 50** has a wide margin of safety when used in overdose. No serious events have been reported following overdoses of **SERDEP 50** of up to 6 g. Although **SERDEP 50** in overdose can not be linked to any deaths, overdoses of **SERDEP 50** 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 50**.
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 50** has a large volume of distribution, hence forced diuresis, dialysis, haemoperfusion, and exchange transfusion will have no benefit.

## IDENTIFICATION

Blue, oblong, film-coated, biconvex tablets with a central breakline on one side and plain on the other.

## PRESENTATION

Blister strips of 10 tablets packed in 30’s.

## STORAGE INSTRUCTIONS

Store in the original packaging, protected from light at a temperature below 25°C.

KEEP OUT OF REACH OF CHILDREN.

## REGISTRATION NUMBER

38/1.2/0020

## NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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