

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DYNA SERTRALINE 50 film coated tablets

DYNA SERTRALINE 100 film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DYNA SERTRALINE 50: Each film coated tablet contains sertraline hydrochloride equivalent to 50 mg sertraline.

DYNA SERTRALINE 100: Each film coated tablet contains sertraline hydrochloride equivalent to 100 mg sertraline.

DYNA SERTRALINE 50 and DYNA SERTRALINE 100 are sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

DYNA SERTRALINE 50 is a blue coloured, capsule shaped, biconvex, film coated tablet debossed with 'SER' on one side and '5' and '0' on either side of the break-line on the other side.

DYNA SERTRALINE 100 is a yellow coloured, capsule shaped,

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biconvex, film coated tablet debossed with 'SER' on one side and '100' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DYNA SERTRALINE is indicated in adults for the treatment of:

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

DYNA SERTRALINE is indicated in children for the treatment of:

- OCD in children aged 13 – 17 years.

Panic disorder: Panic disorder is characterised by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry implications or consequences of the attacks, and/or a significant change in behaviour re 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: palpitations, pounding heart or accelerated heart rate, sweating, trembling or shaking, sensations of shortness of breath or smothering, feeling of choking, chest pain or discomfort,

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nausea or abdominal distress, feeling dizzy, unsteady, light-headed or faint, derealisation (feelings of unreality) or depersonalisation (being detached from oneself), fear of losing control, fear of dying, paraesthesias (numbness or tingling sensations), chills or hot flushes.

The effectiveness of DYNA SERTRALINE in long-term use, that is, for more than 12 weeks, has not been systematically evaluated.

Therefore, the medical practitioner who elects to use DYNA SERTRALINE for extended periods should periodically re-evaluate the long-term usefulness of the medicine for the individual patient (see section 4.2).

4.2 Posology and method of administration

Posology

Adults

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 (OCD):

The minimum effective dose in OCD is 50 mg daily, and increases above 100 mg daily did 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, with or without agoraphobia:

The minimum recommended effective dose of DYNA SERTRALINE

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is 50 mg/day. However, therapy 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.

Special populations

Use in the elderly:

No special precautions are required. The usual adult dosage is recommended.

Use in hepatic and renal impairment:

(See section 4.4 – Use in patients with concomitant illness)

Paediatric population

Obsessive Compulsive Disorder (OCD):

Children and adolescents aged 13 – 17 years:

The administration of DYNA SERTRALINE to paediatric OCD patients (aged 13 - 17 years) should commence at 50 mg/day.

Subsequent doses may be increased in case of lack of response, in 50 mg/day increments, up to 200 mg as needed. However, the generally lower body weights of children compared to adults should be taken into consideration in advancing the dose from 50 mg, in order to avoid excessive dosing. Given the 24-hour elimination half-life of DYNA SERTRALINE, dose changes should not occur at intervals of less than 1 week.

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The use of DYNA SERTRALINE in children and adolescents is not recommended, other than in children between 13 and 17 years with OCD, as safety and efficacy have not been established.

Method of administration

DYNA SERTRALINE should be given as a single daily dose, with or without food.

Discontinuation

If DYNA SERTRALINE therapy has to be discontinued, DYNA SERTRALINE should be tapered. Abrupt discontinuation should be avoided. When stopping treatment with DYNA SERTRALINE, the dose should be gradually reduced over a period of at least one to two weeks, in order to reduce the risk of withdrawal reactions (see section 4.4). If intolerable symptoms occur following a decrease in the dose, or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Missed dose

Doctors should advise patients who forget to take DYNA SERTRALINE to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

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4.3 Contraindications

- Hypersensitivity to sertraline or to any of the ingredients of DYNA SERTRALINE (see section 6.1).
- Concomitant administration with a monoamine oxidase inhibitor (MAOI) is contraindicated (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Concomitant intake of pimozide (see section 4.5).
- Use in hepatic or renal impairment.
- Porphyria.
- Children under the age of 18 years, except for patients with OCD aged 13 - 17 years old (see section 4.4).

4.4 Special warnings and precautions for use

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)

The development of potentially life-threatening syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) has been reported with selective serotonin reuptake inhibitors (SSRIs), including treatment with DYNA SERTRALINE.

The risk of SS or NMS with SSRIs is increased with concomitant use of other serotonergic medicines (including other serotonergic antidepressants, triptans, and fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, meperidine, methadone and pentazocine), with medicines which impair metabolism of serotonin (including MAOIs e.g., methylene blue – see below), antipsychotics and other

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dopamine antagonists, and with opiate medicines. SS symptoms include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Some signs of SS, including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes resemble NMS. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome (see section 4.3).

Monoamine oxidase inhibitors

Cases of serious reactions, sometimes fatal, have been reported in patients receiving sertraline in combination with a MAOI, including selegiline, moclobemide, the antibiotic linezolid and methylene blue. Some cases presented with features resembling SS. Therefore, DYNA SERTRALINE 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 DYNA SERTRALINE treatment and starting a MAOI (see section 4.3).

Switching from Selective Serotonin Re-uptake Inhibitors (SSRIs), antidepressants or anti-obsessional medicines

There is limited controlled experience regarding the optimal timing of switching from SSRIs, antidepressants, or anti-obsessional medicines to DYNA SERTRALINE. Care and prudent medical judgment should be exercised when switching, particularly from long-acting medicines such

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as fluoxetine. The duration of a washout period when switching from one SSRI to another has not been established.

Other serotonergic medicines e.g., tryptophan, fenfluramine and 5-HT agonists

Co-administration of DYNA SERTRALINE with other medicines 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 a pharmacodynamic interaction (see section 4.5).

QTc Prolongation/Torsade de Pointes (TdP)

Cases of QTc prolongation and Torsade de Pointes (TdP) have been reported. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP. Therefore, DYNA SERTRALINE should be used with caution in patients with risk factors for QTc prolongation (see section 4.5).

Activation of hypomania or mania

Manic/hypomanic symptoms have been reported to emerge in a small proportion of patients treated with marketed antidepressant and anti-obsessional medicines, including DYNA SERTRALINE. Therefore, DYNA SERTRALINE should be used with caution in patients with a history of mania/hypomania. Close surveillance by the medical practitioner is required. DYNA SERTRALINE should be discontinued in any patient entering a manic phase.

Schizophrenia

Psychotic symptoms might become aggravated in schizophrenic patients.

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Seizures

Seizures may occur with DYNA SERTRALINE therapy. DYNA SERTRALINE should be avoided in patients with unstable epilepsy. Patients with controlled epilepsy should be carefully monitored. DYNA SERTRALINE should be discontinued in any patient who develops seizures.

Suicide/suicidal thoughts/suicide attempts or clinical worsening

All patients treated with DYNA SERTRALINE, in particular younger patients and those at high risk, should be monitored appropriately and observed closely for clinical worsening and suicidality. Patients, their families, and their caregivers should be encouraged to be alert to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered, especially in depressed patients.

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. The risk may persist until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with DYNA SERTRALINE should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

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Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania and mania). Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing DYNA SERTRALINE, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, DYNA SERTRALINE should be tapered (see section 4.2).

Prescriptions for DYNA SERTRALINE should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

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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. 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 medicines (NSAIDs)) as well as in patients with a history of bleeding disorders (see section 4.5).

Postpartum haemorrhage

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).

Hyponatraemia

Hyponatraemia may occur as a result of treatment with SSRIs or SNRIs, including DYNA SERTRALINE. In many cases, hyponatraemia 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 hyponatraemia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume-depleted, may be at greater risk (see below - Use in elderly). Discontinuation of DYNA SERTRALINE should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatraemia include headache, difficulty concentrating, memory impairment, confusion, weakness

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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.

Bone fractures

Epidemiological studies show an increased risk of bone fractures in patients receiving serotonin reuptake inhibitors (SRIs) including DYNA SERTRALINE. The mechanism leading to this risk is not fully understood.

Withdrawal symptoms seen on discontinuation of DYNA

SERTRALINE treatment

Withdrawal symptoms are common when treatment is discontinued, particularly if discontinuation is abrupt. Studies indicate the incidence of reported withdrawal reactions was 23 % in those discontinuing DYNA SERTRALINE, compared to 12 % in those who continued to receive DYNA SERTRALINE treatment.

The risk of withdrawal symptoms may depend on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sweating, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion and headache are the most commonly reported reactions.

These symptoms may be severe in some patients. They usually occur within the first few days of discontinuing treatment, but there have been reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and may resolve within 2 weeks, though in some individuals these may be prolonged (2-3 months or more). It is therefore advised that DYNA SERTRALINE

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should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

Akathisia/psychomotor restlessness

The use of DYNA SERTRALINE has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hepatic impairment

DYNA SERTRALINE is extensively metabolised 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 C_{max} in comparison to normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of DYNA SERTRALINE in patients with hepatic disease must be approached with caution. If DYNA SERTRALINE is administered to patients with hepatic impairment, a lower or less frequent dose should be considered. DYNA SERTRALINE should not be used in patients with severe hepatic impairment (see section 4.3).

Renal impairment

DYNA SERTRALINE is extensively metabolised, and excretion of unchanged medicine in urine is a minor route of elimination.

In patients with mild to moderate renal impairment (creatinine clearance 20 – 60 mL/min) or severe renal impairment (creatinine clearance < 30

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mL/min), multiple dose pharmacokinetic parameters (AUC or C_{max}) are modest. DYNA SERTRALINE should not be used in patients with renal impairment (see section 4.3).

Use in elderly

The pattern and incidence of adverse reactions in the elderly is similar to that in younger patients.

SSRIs or SNRIs, including DYNA SERTRALINE, have however been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse event (see Hyponatraemia above).

Diabetes

Cases of new onset diabetes mellitus have been reported in patients receiving SSRIs including DYNA SERTRALINE. Loss of glycaemic control including both hyperglycaemia and hypoglycaemia has also been reported in patients with and without pre-existing diabetes. Patients should therefore be monitored for signs and symptoms of glucose fluctuations. Diabetic patients, especially, should have their glycaemic control carefully monitored since their dosage of insulin and/or concomitant oral hypoglycaemic medicine may need to be adjusted.

Electroconvulsive therapy (ECT)

There are no studies establishing the risks or benefits of the combined use of ECT and DYNA SERTRALINE.

Grapefruit juice

The administration of DYNA SERTRALINE with grapefruit juice is not recommended (see section 4.5).

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Interference with urine screening tests

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking DYNA SERTRALINE. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of DYNA SERTRALINE therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish DYNA SERTRALINE from benzodiazepines.

Laboratory abnormalities

Asymptomatic elevations of serum transaminases (AST and ALT) have been reported infrequently in association with DYNA SERTRALINE therapy. The abnormalities usually occur within the first 1 to 9 weeks of treatment and diminish upon discontinuation of the medicine. There have been reports of altered platelet function and/or abnormal clinical laboratory results in patients taking DYNA SERTRALINE.

Angle-closure glaucoma

SSRIs, including DYNA SERTRALINE, may have an effect on pupil size, resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in pre-disposed patients. DYNA SERTRALINE should therefore be used with caution in patients with angle-closure glaucoma or a history of glaucoma.

Weight loss

Significant weight loss may be an undesirable result of treatment with DYNA SERTRALINE for some patients; approximately 0,5 kg – 1,0 kg weight loss.

Weak uricosuric effect

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DYNA SERTRALINE 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 advised in patients with disease or conditions that could affect metabolism or haemodynamic responses, when treated with DYNA SERTRALINE.

Myocardial infarction

DYNA SERTRALINE has not been evaluated, or used to any appreciable extent, in patients with a recent history of myocardial infarction or unstable heart disease.

Interference with cognitive and motor performance

DYNA SERTRALINE does not cause sedation and does not interfere with psychomotor performance.

Porphyria

DYNA SERTRALINE is considered to be unsafe in patients with porphyria because it might be porphyrinogenic.

Paediatric population

The safety and efficacy of DYNA SERTRALINE has been established in paediatric patients (aged 13 - 17 years) with obsessive-compulsive disorder (OCD). The safety and efficacy in children under 18 years of age, other than those with OCD, have not been established (see section 4.3).

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

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In Major Depressive Disorder clinical trials, there were increased reports of hostility and suicide – related adverse events such as suicidal ideation and self-harm (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Concomitant use contraindicated

- **Monoamine Oxidase Inhibitors (e.g., selegiline, moclobemide and linezolid):** DYNA SERTRALINE must not be used in combination with irreversible MAOIs such as selegiline, moclobemide and linezolid. DYNA SERTRALINE must not be initiated for at least 14 days after discontinuation of treatment with a MAOI, and must be discontinued for at least 7 days before starting treatment with a MAOI (see section 4.3).

Severe adverse reactions have been reported in patients who have recently been discontinued from a MAOI (e.g. methylene blue) and started on DYNA SERTRALINE, or have recently had DYNA SERTRALINE therapy discontinued prior to initiation of a MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death.

- **Pimozide:** Increased pimozide plasma levels have been observed in a clinical study after concomitant administration of sertraline and a low single dose of pimozide (2 mg). These increased levels have not been associated with ECG-changes. The mechanism of this interaction is unknown. The concomitant

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administration of DYNA SERTRALINE and pimozide is contraindicated, because co-administration results in increased pimozide plasma levels, and as a consequence may increase the risk of dysrhythmias and prolongation of QT-interval associated with pimozide treatment (see section 4.3).

Concomitant use not recommended

- **CNS depressants and alcohol:** Although concomitant use of sertraline 200 mg daily did not potentiate the effects of alcohol, carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects, DYNA SERTRALINE and alcohol in depressed patients is not recommended.
- **Grapefruit juice:** A study indicates that the intake of three glasses of grapefruit juice daily increased the sertraline plasma levels by approximately 100 %. Therefore, the intake of grapefruit juice should be avoided during treatment with DYNA SERTRALINE (see section 4.4).
- **St John's Wort (*Hypericum perforatum*):** Concomitant use of the herbal remedy St John's Wort (*Hypericum perforatum*) in patients receiving SSRIs should be avoided, since there is a possibility of serotonergic potentiation.
- **Serotonergic medicines:** Co-administration of DYNA SERTRALINE with other medicines which enhance serotonergic neurotransmission, such as tryptophan or fenfluramine, should be avoided due to the potential for pharmacodynamic interaction.

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Caution is also advised with fentanyl (used in general anaesthesia or in the treatment of chronic pain), other serotonergic medicines (including other serotonergic antidepressants, triptans), and with other opiate medicines.

- **CYP3A4 inhibitors:** Based on the interaction study with grapefruit juice, it cannot be excluded that the concomitant administration of DYNA SERTRALINE and potent CYP3A4 inhibitors, e.g., protease inhibitors, ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin and nefazodone, would result in even larger increases in exposure of DYNA SERTRALINE. This also concerns moderate CYP3A4 inhibitors, e.g., aprepitant, erythromycin, fluconazole, verapamil and diltiazem. The intake of potent CYP3A4 inhibitors should be avoided during treatment with DYNA SERTRALINE.

Special precautionary monitoring is advised

- **Medicines that prolong the QTc interval:** The risk of QTc prolongation and/or ventricular dysrhythmias (e.g. TdP) is increased with concomitant use of other medicines that prolong the QTc interval (e.g. some antipsychotics and antibiotics) (see sections 4.4 and 5.1).
- **Lithium:** It is recommended that plasma lithium levels be monitored following initiation of DYNA SERTRALINE 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

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interaction. Therefore, caution is recommended when co-administering DYNA SERTRALINE with medicines such as lithium, which may act via serotonergic mechanisms.

- **Triptans**

Sumatriptan: Cases of weakness, hyperreflexia, incoordination, confusion, anxiety and agitation have been reported in association with the concomitant use of sertraline and sumatriptan. Symptoms of serotonergic syndrome may also occur with other medicines of the same class (triptans). If concomitant treatment with DYNA SERTRALINE and triptans is clinically warranted, appropriate observation of the patient is advised (see section 4.4).

- **Phenytoin:** Reports of high phenytoin exposure in patients using DYNA SERTRALINE have emerged; it is recommended that plasma phenytoin concentrations be monitored following initiation of DYNA SERTRALINE, with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of DYNA SERTRALINE plasma levels. It cannot be excluded that other CYP3A4 inducers, e.g., phenobarbital, carbamazepine, St John's Wort, rifampicin may cause a reduction of DYNA SERTRALINE plasma levels.
- **Protein bound medicine:** DYNA SERTRALINE is highly bound to serum proteins (98 %) in the range 20 to 500 ng/mL. However, at up to 300 to 200 ng/mL concentrations, respectively, DYNA SERTRALINE and N-

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desmethylsertraline do not alter the plasma protein binding of two other highly protein bound medicines, viz. warfarin and propranolol. However, in interaction with diazepam, tolbutamide and warfarin respectively, DYNA SERTRALINE has no significant effects on the protein binding of the substrate (see Other Interactions below).

- **Switching from other antidepressants or anti-obsessional medicines:**

There is limited controlled experience regarding the optimal timing of switching from other antidepressants or anti-obsessional medicines to DYNA SERTRALINE. Care and prudent medical judgement should be exercised when switching, particularly from long-acting medicines such as fluoxetine. The duration of washout period which should intervene before switching from one selective serotonin re-uptake inhibitor (SSRI) to another has not been established (see section 4.4).

- **Other interactions:** Co-administration of

DYNA SERTRALINE with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters. Co-administration with cimetidine caused substantial decrease in DYNA SERTRALINE clearance. The clinical significance of these changes is unknown.

- **Oral anticoagulants, salicylic acid derivatives and NSAIDs:** On

concomitant administration of sertraline and warfarin there was a slight, but statistically significant, increase in prothrombin time; close monitoring of prothrombin time is thus advisable when therapy with DYNA SERTRALINE is

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initiated or terminated. There may potentially be an increased risk of bleeding when SSRIs are combined with other oral anticoagulants, salicylic acid derivatives, NSAIDs, atypical antipsychotics, phenothiazines and most tricyclic antidepressants (see section 4.4).

- **Hypoglycaemic medicines:** Sertraline, as in DYNA SERTRALINE, may alter glycaemic control. Therefore, it is advisable to monitor blood glucose levels when initiating DYNA SERTRALINE for diabetic patients (see section 4.4).
- **Diuretics:** Diuretics used concomitantly with sertraline may predispose elderly patients to hyponatraemia and SIADH (syndrome of inappropriate antidiuretic hormone).
- **CYP2C19 inhibitors:** Sertraline plasma levels are enhanced by about 50 % in poor metabolisers of CYP2C19 compared to rapid metabolisers (see Pharmacokinetic properties). Interaction with strong inhibitors of CYP2C19, e.g., omeprazole, lansoprazole, pantoprazole, rabeprazole, fluoxetine, fluvoxamine cannot be excluded.
- **Antivirals:** Plasma concentrations of DYNA SERTRALINE may be increased by HIV protease inhibitors such as ritonavir.

No interactions reported

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

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- **Medicines metabolised by cytochrome P450 (CYP) 2D6:**

There is variability among antidepressants in the extent of clinically important inhibition of the medicine metabolising isoenzyme CYP 2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered medicine. CYP 2D6 substrates with a narrow therapeutic index include tricyclic antidepressants (TCAs) and class 1C anti-dysrhythmics such as propafenone and flecainide. In formal interaction studies, chronic dosing with DYNA 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:** Chronic administration of DYNA SERTRALINE 200 mg daily does not inhibit the CYP 3A3/4 mediated 6- β hydroxylation of endogenous cortisol or the metabolism of carbamazepine. In addition, the chronic administration of DYNA SERTRALINE 50 mg daily does not inhibit the CYP 3A3/4 mediated metabolism of alprazolam.

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

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4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should employ an adequate method of contraception when taking DYNA SERTRALINE.

Pregnancy

The safety of DYNA SERTRALINE during pregnancy has not been established (see section 4.3).

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Breastfeeding

The safety of DYNA SERTRALINE during pregnancy and lactation has not been established (see section 4.3).

Fertility

There is no clinical trial data on fertility. In animal studies, no effect on fertility parameters was observed.

4.7 Effects on ability to drive and use machines

DYNA SERTRALINE has no effect on psychomotor performance. However, patients should be cautioned accordingly when driving a car or operating machinery.

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4.8 Undesirable effects

Summary of the safety profile

Nausea is the most common undesirable effect. In the treatment of social anxiety disorder, sexual dysfunction (ejaculation failure) in men occurred in 14 % for sertraline vs 0 % in placebo. These undesirable effects are dose dependent and are often transient in nature with continued treatment.

The undesirable effects profile commonly observed in double-blind, placebo-controlled studies in patients with OCD, panic disorder, PTSD and social anxiety disorder was similar to that observed in clinical trials in patients with depression.

Some adverse drug reactions listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Tabulated summary of adverse reactions

| System Organ Class | Frequency | Side effects |
|---|---------------------------|---|
| Infections and infestations | Frequent Less frequent | Pharyngitis Upper respiratory tract infection, rhinitis, diverticulitis, gastroenteritis, otitis media |
| Neoplasms benign and malignant (including cysts and polyps) | Less frequent | Neoplasm |

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| | | |
|--------------------------------------|--|--|
| Blood and lymphatic system disorders | Frequent Less frequent Frequency unknown | Lymphadenopathy Agranulocytosis, aplastic anaemia, increased coagulation times, leukopenia, pancytopenia, thrombocytopenia, hyponatraemia Abnormal platelet function test* |
| Immune system disorders | Less frequent Frequency unknown | Hypersensitivity, anaphylactoid reaction, serum-sickness Allergy, angioedema, seasonal allergy* |
| Endocrine disorders | Less frequent Frequency unknown | Hypothyroidism Hyperprolactinaemia, Syndrome of inappropriate anti-diuretic hormone secretion (SIADH) |
| Metabolism and nutrition disorders | Frequent Less frequent Frequency unknown | Weight loss, decreased appetite, increased appetite Diabetes mellitus, hypercholesterolaemia, hypoglycaemia, hyperprolactinaemia Hyponatraemia, hyperglycaemia |

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| Psychiatric disorders | Frequent | Nervousness, depression, depersonalisation, nightmare, anxiety, agitation, libido decreased, bruxism |
| | Less frequent | Hallucination, aggression, euphoria, apathy, abnormal thinking, conversion disorder, medicine dependence, psychosis, mania, hypomania, paranoia, suicidal ideation/behaviour, sleep walking, impaired concentration |
| | Frequency unknown | Paranoia, confusional state*, euphoric mood*, psychotic disorder* |

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| Nervous system disorders | Frequent | Headache, dizziness, tremor, insomnia, somnolence, paraesthesia, hypertonia, dysgeusia |
| | Less frequent | Hypoaesthesia, twitching, seizures, convulsion, involuntary muscle contractions, abnormal coordination, hyperkinesia, amnesia, speech disorder, postural dizziness, syncope, migraine, coma, choreoathetosis, dyskinesia, hyperaesthesia, sensory disturbance |
| | Frequency unknown | Movement disorders (including extrapyramidal symptoms such as hypertonia, dystonia, teeth grinding or gait abnormalities), serotonin syndrome, neuroleptic malignant syndrome, cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome) |
| Eye disorders | Frequent | Visual disturbances |
| | Less frequent | Mydriasis, glaucoma, lacrimal disorder, scotoma, diplopia, photophobia, hyphaemia |
| | Frequency unknown | Abnormal vision, pupils unequal, optic neuritis, cataract, periorbital oedema* |
| Ear and labyrinth disorders | Frequent | Tinnitus |
| | Less frequent | Ear pain |

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| Cardiac disorders | <p>Frequent</p> <p>Less frequent</p> <p>Frequency unknown</p> | <p>Palpitations</p> <p>Tachycardia, bradycardia, cardiac disorder, atrial dysrhythmias, atrioventricular block, myocardial infarction</p> <p>QT prolongation, Torsades de Pointes, increased blood cholesterol*</p> |
| Vascular disorders | <p>Frequent</p> <p>Less frequent</p> <p>Frequency unknown</p> | <p>Hot flush</p> <p>Pulmonary hypertension, flushing, peripheral ischaemia, haematuria, hypotension</p> <p>Abnormal bleeding</p> |
| Respiratory, thoracic and mediastinal disorders | <p>Frequent</p> <p>Less frequent</p> <p>Frequency unknown</p> | <p>Yawning</p> <p>Bronchospasm, dyspnoea, epistaxis, laryngospasm, hyperventilation, hypoventilation, stridor, dysphonia, hiccups</p> <p>Interstitial lung disease</p> |

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| Gastrointestinal disorders | Frequent | Nausea, diarrhoea, dyspepsia, anorexia, vomiting, flatulence, dry mouth, constipation, abdominal pain |
| | Less frequent | Oesophagitis, dysphagia, haemorrhoids, salivary hypersecretion, tongue disorder, eructation, melaena, haematochezia, stomatitis, tongue ulceration, tooth disorder, glossitis, mouth ulceration |
| | Frequency unknown | Pancreatitis, gastrointestinal haemorrhage* |
| Hepatobiliary disorders | Less frequent | Hepatotoxicity, jaundice, liver failure, hepatitis, hepatomegaly |
| | Frequency unknown | Increased alanine aminotransferase*, increased aspartate aminotransferase*, liver injury* |
| Skin and subcutaneous tissue disorders | Frequent | Rash, increased sweating, hyperhidrosis |
| | Less frequent | Periorbital oedema, face oedema, purpura, alopecia, cold sweat, dry skin, urticaria, pruritus, dermatitis, dermatitis bullous, rash follicular, hair texture abnormal, skin odour abnormal |
| | Frequency unknown | Lupus-like syndrome, Stevens Johnson syndrome, vasculitis, epidermal necrolysis, photosensitivity, skin reaction, angioedema*, exfoliative rash* |

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| Musculoskeletal, connective tissue and bone disorders | Frequent Less frequent Frequency unknown | Arthralgia, myalgia Osteoarthritis, muscular weakness, back pain, muscle twitching, bone disorder Muscle cramps, increased risk of bone fractures, trismus*, rhabdomyolysis* |
| Renal and urinary disorders | Less frequent | Nocturia, urinary retention, polyuria, pollakiuria, micturition disorder, urinary incontinence, oliguria, urinary hesitation, urinary tract infection, acute renal failure, micturition frequency |
| Reproductive system and breast disorders | Frequent Less frequent Frequency unknown | Ejaculation delay, ejaculation failure Menstrual symptoms, vaginal haemorrhage, sexual dysfunction, female sexual dysfunction, menstruation irregular, menorrhagia, atrophic vulvovaginitis, balanoposthitis, genital discharge, priapism, galactorrhoea, hyperprolactinaemia, premature ejaculation Gynaecomastia, postpartum haemorrhage |
| General disorders and administrative site conditions | Frequent Less frequent Frequency unknown | Fever, fatigue, malaise, chest pain Oedema peripheral, chills, pyrexia, asthenia, thirst, hernia, medicine tolerance decreased, Face oedema* |

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| Investigations | Less frequent Frequency unknown | Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased, weight increased, semen abnormal, blood cholesterol increased Abnormal clinical laboratory results, altered platelet function |
| Injury and poisoning | Less frequent Frequency unknown | Injury Fracture* |
| Surgical and medical procedures | Less frequent | Vasodilation procedure |

*Post marketing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: <https://www.sahpra.org.za/Publications/Index/8>.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Symptoms of overdose may include electrocardiogram QT

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prolonged, TdP (see sections 4.4, 4.5 and 5.1), drowsiness, nausea and vomiting, rapid heart rate, shaking, agitation, dizziness and in rare cases, unconsciousness.

Deaths have been reported involving overdoses of sertraline, primarily in combination with other medicines and/or alcohol. Therefore, any overdosage should be treated aggressively.

Management of overdose:

No specific therapy is recommended and there are no specific antidotes to DYNA SERTRALINE. Establish and maintain an open airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, a cathartic, may be as, or more, effective than emesis 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 DYNA SERTRALINE, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors

(SSRI)

ATC code: N06 AB06

Pharmacological classification: A.1.2 Psychoanaleptics

(Antidepressants)

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Mechanism of action

Sertraline is a specific inhibitor of neuronal serotonin re-uptake and has only very weak effects on the norepinephrine and dopamine neuronal re-uptake. The mechanism of action of sertraline is presumed to be linked to the inhibition of central nervous system neuronal uptake of serotonin (5-HT). Sertraline blocks the uptake of serotonin into human platelets.

Sertraline is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. Sertraline does not enhance catecholaminergic activity and it has no affinity for cholinergic, serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT₂), dopaminergic, adrenergic (alpha-1, alpha-2, beta) histaminergic, GABA or benzodiazepine receptors.

The chronic administration of sertraline in animals was associated with downregulation of brain norepinephrine (noradrenaline) receptors.

Cardiac electrophysiology

In a dedicated thorough QTc study, conducted at steady-state at supra-therapeutic exposures in healthy volunteers (treated with 400 mg/day, twice the maximum recommended daily dose), the upper bound of the 2-sided 90 % CI for the time matched Least Square mean difference of QTcF between sertraline and placebo (11,666 msec) was greater than the predefined threshold of 10 msec at the 4-hour post dose time point. Exposure-response analysis indicated a relationship between QTcF and sertraline plasma concentrations [0,036 msec/(ng/mL); $p < 0,0001$] (see sections 4.4, 4.5, 4.8 and 4.9).

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5.2 Pharmacokinetic properties

Absorption:

Following an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of sertraline occur at 4,5 to 8,4 hours after the daily administration. Food does not significantly change the bioavailability of sertraline tablets.

Distribution:

Approximately 98 % of the circulating medicine is bound to plasma proteins.

Biotransformation:

Sertraline undergoes extensive first-pass hepatic metabolism. Based on clinical and *in-vitro* data, it can be concluded that sertraline is metabolised by multiple pathways including CYP3A4, CYP2C19 (see section 4.5) and CYP2B6. Sertraline and its major metabolite desmethylsertraline are also substrates of P-glycoprotein *in-vitro*.

Both *in vitro* biochemical and *in vivo* pharmacological testing have shown the principal metabolite, N-desmethylsertraline, to have significantly less clinical activity.

Elimination:

The mean half-life of sertraline is approximately 26 hours (range 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 one week of once-daily dosing. The terminal half-life of N-desmethylsertraline is in the range of 62 to 104 hours. Both sertraline and N-desmethylsertraline are extensively metabolised and the resultant metabolites excreted in faeces and urine in equal amounts. Only a small amount (< 0,2 %) of unchanged sertraline is excreted in the urine.

Linearity/non-linearity:

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Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg.

Desmethylsertraline exhibits time related dose dependent increases in AUC, C_{max} and C_{min} , with a 5 to 9-fold increase in these parameters between day 1 and day 14.

Pharmacokinetics in special patient groups

Adolescents and elderly:

Sertraline plasma clearance in elderly patients is approximately 40 % lower than in younger (25 - 32 year old) individuals. Steady state, therefore, should be achieved after 2 to 3 weeks in older patients.

There is a decreased clearance of desmethylsertraline in older males, but not in older females.

Hepatic impairment:

In patients with liver damage, the half-life of sertraline is prolonged and AUC is increased three-fold (see sections 4.2 and 4.4).

Renal impairment:

In patients with moderate to severe renal impairment, there was no significant accumulation of sertraline.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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Tablet cores:

Dibasic calcium phosphate anhydrous

Hydroxypropyl cellulose

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate

Film Coating:

DYNA SERTRALINE 50: Opadry blue

FD&C blue #2/indigo carmine aluminium lake

Hypromellose

Macrogol

Polysorbate

Titanium dioxide

DYNA SERTRALINE 100: Opadry yellow

Hypromellose

Iron oxide yellow

Macrogol

Polysorbate

Titanium dioxide

6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

Do not remove tablets from outer carton until required for use.

6.5 Nature and contents of container

DYNA SERTRALINE tablets are packed in white opaque PVC/PVDC and aluminium blister strips containing 30 tablets. The blister will be placed in an outer carton bearing the labelling requirements.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

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8. REGISTRATION NUMBER(S)

DYNA SERTRALINE 50: A43/1.2/0339

DYNA SERTRALINE 100: A43/1.2/0340

9. DATE OF FIRST AUTHORISATION

05 December 2013

10. DATE OF REVISION OF THE TEXT

13 October 2023

NAMIBIA

DYNA SERTRALINE 50: NS3 14/1.2/0627

DYNA SERTRALINE 100: NS3 14/1.2/0628