DYNA SERTRALINE

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, 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 about the implications or consequences of the attacks, and/or a significant change in behaviour related to the attacks.
Panic disorder is characterised by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: 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, 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, paraesthesia (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:
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 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:
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.

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.

4.3 Contraindications

- Hypersensitivity to sertraline or to any of the ingredients of DYNA SERTRALINE.
- 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).
- Severe hepatic impairment.
- Porphyria.
- Children under the age of 18 years, except for patients with obsessive compulsive disorder 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), with medicines which impair metabolism of serotonin (including MAOIs e.g., methylene blue), antipsychotics and other dopamine antagonists, and with opiate medicines. Patients should be monitored for the emergence of signs and symptoms of SS or NMS (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 as fluoxetine.

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, fenfluramine, 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.

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.

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.

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
Patients with major depressive disorders, 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.

Because of the possibility of co-morbidity between major depressive disorders 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 disorders 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.

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/Serotonin and Norepinephrine Reuptake Inhibitors (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 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 and unsteadiness which may lead to falls. Signs and symptoms associated with more severe and/or acute cases include hallucination, syncope, seizure, coma, respiratory arrest and death.

Withdrawal symptoms seen on discontinuation of DYNA SERTRALINE treatment
Withdrawal symptoms are common when treatment with DYNA SERTRALINE 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 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 mL/min), multiple dose pharmacokinetic parameters (AUC or C_{max}) are modest. DYNA SERTRALINE should be used with care in these patients. The dose of DYNA SERTRALINE may have to be reduced in patients with impaired renal function.

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
In patients with diabetes, treatment with DYNA SERTRALINE may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage 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).

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
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 diseases 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 have 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.
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

- **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 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).
- **CNS depressants and alcohol:** Concomitant use of DYNA SERTRALINE and alcohol is not recommended.

Special precautionary monitoring is advised with the following:
- **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-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).
- **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.
  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.
- **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 have emerged of high phenytoin exposure in patients using DYNA SERTRALINE; 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 (*Hypericum perforatum*), rifampicin may cause a reduction of DYNA SERTRALINE plasma levels.
- **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).
- **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.

- **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 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).
- **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 interaction. Therefore, caution is recommended when co-administering DYNA SERTRALINE with medicines such as lithium, which may act via serotonergic mechanisms.
- **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).
- **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).
- **CYPA34 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.
- **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 with the following:
- 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.
- **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 and, 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-α hydroxylation of endogenous cortisol or the metabolism of carbamazepine.
- 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.

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).

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.

4.8 Undesirable effects

a) Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Infections and infestations	*Frequent*	Pharyngitis
	Less frequent	Upper respiratory tract infection, rhinitis, diverticulitis, gastroenteritis, otitis media
Neoplasms benign and malignant (including cysts and polyps)	*Less frequent*	Neoplasm
Blood and lymphatic system disorders	*Frequent*	Lymphadenopathy
	Less frequent	Agranulocytosis, aplastic anaemia, increased coagulation times, leukopenia, pancytopenia, thrombocytopenia, hyponatraemia
Immune system disorders	*Less frequent*	Hypersensitivity, anaphylactoid reaction, serum-sickness
	Frequency unknown	Allergy, angioedema
Endocrine disorders	*Less frequent*	Hypothyroidism
	Frequency unknown	Hyperprolactinaemia, Syndrome of inappropriate anti diuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	*Frequent*	Weight loss, decreased appetite, increased appetite
	Less frequent	Diabetes mellitus, hypercholesterolaemia, hypoglycaemia, hyperprolactinaemia
	Frequency unknown	Hyperglycaemia
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
Nervous system disorders	*Frequent*	Headache, dizziness, tremor, insomnia, somnolence, paraesthesia, hypertonia, dysgeusia
	Less frequent	Hypoaesthesia, twitching, seizures, convulsion, involuntary muscle contractions, abnormal co-ordination, 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, hyphema
	Frequency unknown	Abnormal vision, pupils unequal, optic neuritis, cataract
Ear and labyrinth disorders	*Frequent*	Tinnitus
	Less frequent	Ear pain
Cardiac disorders	*Frequent*	Palpitations
	Less frequent	Tachycardia, bradycardia, cardiac disorder, atrial dysrhythmias, atrioventricular block, myocardial infarction
	Frequency unknown	QT prolongation, *Torsades de pointes*
Vascular disorders	*Frequent*	Hot flush
	Less frequent	Pulmonary hypertension, flushing, peripheral ischaemia, haematuria, hypotension
	Frequency unknown	Abnormal bleeding
Respiratory, thoracic and mediastinal disorders	*Frequent*	Yawning
	Less frequent	Bronchospasm, dyspnoea, epistaxis, laryngospasm, hyperventilation, hypoventilation, stridor, dysphonia, hiccups
	Frequency unknown	Interstitial lung disease
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
Hepato-biliary disorders	*Less frequent*	Hepatotoxicity, jaundice, liver failure, hepatitis, hepatomegaly
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, follicular rash, hair texture abnormal, skin odour abnormal
	Frequency unknown	Lupus-like syndrome, Stevens-Johnson syndrome, vasculitis, epidermal necrolysis, photosensitivity, skin reaction
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Arthralgia, myalgia
	Less frequent	Osteoarthritis, muscular weakness, back pain, muscle twitching, bone disorder
	Frequency unknown	Muscle cramps, increased risk of bone fractures
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*	Ejaculation delay, ejaculation failure
	Less frequent	Menstrual symptoms, vaginal haemorrhage, sexual dysfunction, female sexual dysfunction, menstruation irregular, menorrhagia, atrophic vulvovaginitis, balanoposthitis, genital discharge, priapism, galactorrhoea, hyperprolactinaemia, premature ejaculation
	Frequency unknown	Gynaecomastia, postpartum haemorrhage
General disorders and administrative site conditions	*Frequent*	Fever, fatigue, malaise, chest pain
	Less frequent	Oedema peripheral, chills, pyrexia, asthenia, thirst, hernia, medicine tolerance decreased
Investigations	*Less frequent*	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased, weight increased, semen abnormal, blood cholesterol increased
	Frequency unknown	Abnormal clinical laboratory results, altered platelet function
Injury and poisoning	*Less frequent*	Injury
Surgical and medical procedures	*Less frequent*	Vasodilation procedure

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8".

4.9 Overdose

Signs and symptoms:
Symptoms of overdose may include drowsiness, nausea and vomiting, rapid heart rate, shaking, agitation, dizziness and in rare cases, unconsciousness.

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)

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 ($5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_2$), dopaminergic, adrenergic (alpha-1, alpha-2, beta) histaminergic, GABA or benzodiazepine receptors.

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:
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 to 32 year old) individuals. Steady state, therefore, should be achieved after 2 to 3 weeks in older patients. There is a decreased clearance of N-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-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

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.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ºC 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

8. REGISTRATION NUMBERS

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

30 September 2021

NAMIBIA:
DYNA SERTRALINE 50: NS3 14/1.2/0627
DYNA SERTRALINE 100: NS3 14/1.2/0628