

For the use only of a Registered Medical Practitioner (Psychiatrist), or a Hospital, or a Laboratory.

(Sertraline tablets I.P.)

DAXID[®] Tablets



1. NAME OF MEDICINAL PRODUCT

DAXID

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Daxid is available as film-coated tablets for oral administration containing Sertraline Hydrochloride I.P. equivalent to 25 mg, 50 mg or 100 mg Sertraline.

For full list of excipients please see section 6.1.

All strengths/presentations mentioned in this document might not be available in the market.

3. PHARMACEUTICAL FORM

Film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sertraline is indicated for the treatment of symptoms of depression, including depression accompanied by symptoms of anxiety, in patients with or without a history of mania. Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes.

Sertraline is indicated for the treatment of obsessive-compulsive disorder (OCD). Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of OCD.

Sertraline is indicated for the treatment of pediatric patients with OCD.

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DAXID Tablets

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Sertraline is indicated for the treatment of panic disorder, with or without agoraphobia. Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of panic disorder.

Sertraline is indicated for the treatment of post-traumatic stress disorder (PTSD). Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of initial episode of PTSD.

Sertraline is indicated for the treatment of social phobia (social anxiety disorder). Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of social phobia.

Sertraline is indicated for the treatment of premenstrual dysphoric disorder (PMDD).

4.2 Posology and Method of Administration

Sertraline film-coated tablets should be administered once daily, either in the morning or evening.

Sertraline film-coated tablets can be administered with or without food.

Initial Treatment

Depression and OCD

Sertraline treatment should be administered at a dose of 50 mg/day.

Panic Disorder, PTSD and Social Phobia

Therapy should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.

PMDD

Sertraline treatment should be initiated with a dose of 50 mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.

Titration

Depression, OCD, Panic Disorder, and PTSD

Patients not responding to a 50 mg dose may benefit from dose increases. Dose changes should be made at intervals of at least one week, up to a maximum of 200 mg/day. Changes in dose should not be made more frequently than once per week given the 24-hour elimination half life of sertraline.

The onset of therapeutic effect may be seen within 7 days. However, longer periods are usually necessary to demonstrate therapeutic response, especially in OCD.

PMDD

Patients not responding to a 50 mg/day dose may benefit from dose increases (at 50 mg increments/menstrual cycle) up to 150 mg/day when dosing daily throughout the menstrual cycle, or 100 mg/day when dosing during the luteal phase of the menstrual cycle. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilized at the beginning of each luteal phase dosing period.

Maintenance

Dosage during long-term therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response. In PMDD, the effectiveness of sertraline in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. However, as women commonly report that symptoms worsen with age until relieved by the onset of menopause, it is reasonable to consider continuation of a responding patient. Dosage adjustments, which may include changes between dosage regimens (e.g., daily throughout the menstrual cycle versus during the luteal phase of the menstrual cycle), may be needed to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Use in Children

The safety and efficacy of sertraline have been established in pediatric OCD patients aged 6 to 17 years. The administration of sertraline to pediatric OCD patients (aged 13 to 17 years) should commence at 50 mg/day. Therapy for pediatric OCD patients (aged 6 to 12 years) should commence at 25 mg/day, increasing to 50 mg/day after one week. Subsequent doses may be increased in case of lack of response in 50 mg/day increments, up to 200 mg/day, as needed. In a clinical trial in patients aged 6 to 17 years with depression or OCD, sertraline appeared to have a similar pharmacokinetic profile to that found in adults. However, the generally lower body weights of children compared to those of adults should be taken into consideration when increasing the dose from 50 mg.

Titration in Children and Adolescents

Sertraline has an elimination half-life of approximately one day; dose changes should not occur at intervals of less than one week.

Use in the Elderly

The same dose range as in younger patients may be used in the elderly. Over 700 elderly patients (>65 years) have participated in clinical studies that demonstrated the efficacy of sertraline in this patient population. The pattern and incidence of adverse reactions in the elderly were similar to that in younger patients.

Use in Hepatic Insufficiency

The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment (see section 4.4. – **Special Warnings and Special Precautions for Use**).

Use in Renal Insufficiency

Sertraline is extensively metabolized. Excretion of unchanged drug in urine is a minor route of elimination. As expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment (see section **4.4. – Special Warnings and Special Precautions for Use**).

4.3 Contraindications

Sertraline is contraindicated in patients with a known hypersensitivity to sertraline.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see section **4.4. – Special Warnings and Special Precautions for Use**).

Concomitant use in patients taking pimozide is contraindicated (see section **4.5. – Interaction with Other Medicaments and Other Forms of Interaction**).

4.4 Special Warnings and Precautions for Use

Serotonin Syndrome or Neuroleptic Malignant Syndrome

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 sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of serotonergic drugs (including amphetamines, triptans and fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, meperidine, methadone, pentazocine), with drugs that impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. SS symptoms may 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, diarrhea). 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 – Contraindications**).

Monoamine Oxidase Inhibitors

Cases of serious reactions, sometimes fatal, have been reported in patients receiving sertraline in combination with a MAOI, including the selective MAOI selegiline, the reversible MAOI moclobemide, and MAOI drugs, e.g., linezolid (an antibiotic that is a reversible non-selective MAOI) and methylene blue. Some cases presented with features resembling SS, the symptoms of which include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. Therefore, sertraline should not be used in combination with an MAOI or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should elapse after discontinuing sertraline treatment before starting an MAOI (see section **4.3. – Contraindications**).

Other Serotonergic Drugs

Co-administration of sertraline with other drugs that enhance the effects of serotonergic neurotransmission, such as amphetamines, tryptophan, fenfluramine, fentanyl, 5-HT agonists, or the herbal medicine St. John's Wort (*Hypericum perforatum*) should be undertaken with caution and avoided whenever possible due to potential for pharmacodynamic interaction.

QTc Prolongation/Torsade de Pointes (TdP)

Cases of QTc prolongation and TdP have been reported during post-marketing use of sertraline. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP. Therefore, sertraline should be used with caution in patients with risk factors for QTc prolongation (see sections 4.5 – Interaction with other medicinal products and other forms of interaction and 5.1 – Pharmacodynamic properties).

Diabetes/Loss of Glycemic Control – Cases of new onset diabetes mellitus have been reported in patients receiving SSRIs including sertraline. Loss of glycemic control including both hyperglycemia and hypoglycemia 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 glycemic control carefully monitored since their dosage of insulin and/or concomitant oral hypoglycemic drug may need to be adjusted.

Switching from Selective Serotonin Reuptake Inhibitors, Antidepressants or Antiobsessional Drugs

There is limited controlled experience regarding the optimal timing of switching from SSRIs, antidepressants or antiobsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents such as fluoxetine. The duration of a washout period for switching from one SSRI to another has not been established.

Activation of Mania/Hypomania

During pre-marketing testing, hypomania or mania occurred in approximately 0.4% of sertraline-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder treated with other marketed antidepressant and antiobsessional drugs.

Seizures

Seizures are a potential risk with antidepressant and antiobsessional drugs. Seizures were reported in approximately 0.08% of patients treated with sertraline in the development program for depression. No seizures were reported in patients treated with sertraline in the development program for panic. During the development program for OCD, four out of approximately 1,800 patients exposed to sertraline experienced seizures (approximately 0.2%). Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. In all these cases, the relationship with sertraline therapy was uncertain. Since sertraline has not been evaluated in patients with a seizure disorder, it should be avoided in patients with unstable epilepsy; patients with controlled epilepsy

should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

Suicide/Suicidal Thoughts or Clinical Worsening

All patients treated with sertraline, in particular 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 behavior or thoughts and unusual changes in behavior 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, and the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Pooled analyses of short-term placebo controlled trials of antidepressant medicines (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (aged 18 to 24 years) with major depression and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults aged 65 years and older.

Abnormal Bleeding/Haemorrhage

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura to life-threatening hemorrhage with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function [e.g., atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)] as well as in patients with a history of bleeding disorders (see section **4.5. – Interaction with Other Medicaments and Other Forms of Interaction**).

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) including sertraline. In many cases, hyponatremia 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 hyponatremia with SSRIs and SNRIs. Also patients taking diuretics or who are otherwise volume-depleted may be at greater risk (see section **4.2. – Posology and Method of Administration - Use in the Elderly**). Discontinuation of sertraline should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness that 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.

Because of the well-established co-morbidity between OCD and depression, panic disorder and depression, PTSD and depression, and social phobia and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD, panic disorder, PTSD or social phobia.

Bone Fractures

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

Use in Hepatic Insufficiency

Sertraline is extensively metabolized 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 sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.

Use in Renal Insufficiency

Sertraline is extensively metabolized. Excretion of unchanged drug in urine is a minor route of elimination. In studies of patients with mild to moderate renal impairment (creatinine clearance 30-60 mL/min) or moderate to severe renal impairment (creatinine clearance 10-29 mL/min), multiple-dose pharmacokinetic parameters (AUC_{0-24} or C_{max}) were not significantly different compared to controls. Half-lives were similar and there were no differences in plasma protein binding in all groups studied. This study indicates that, as expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Laboratory Tests

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking 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 sertraline therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines.

Angle-closure Glaucoma

SSRIs including 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 patients pre-disposed. Sertraline should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Use in Children and Adolescents

Only limited clinical evidence is available concerning long-term safety data in children and adolescents, including effects on growth, sexual maturation and cognitive and behavioral developments (see section **5.3. Preclinical Safety Data**). Physicians must monitor pediatric patients on long term treatment for abnormalities in growth and development.

4.5 Interaction with Other Medicaments and Other Forms of Interaction

Monoamine Oxidase Inhibitors – (See sections 4.3 – **Contraindications**, and 4.4 – **Special Warnings and Precautions for Use**.)

Pimozide

Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) with sertraline co-administration. These increased levels were not associated with any changes in electrocardiogram (EKG). While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated.

Drugs that Prolong the QTc Interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g., TdP) is increased with concomitant use of other drugs that prolong the QTc interval (e.g., some antipsychotics and antibiotics) (see sections 4.4 – **Special Warnings and Special Precautions for Use** and **5.1 – Pharmacodynamic properties**).

CNS Depressants and Alcohol

The co-administration of sertraline 200 mg daily did not potentiate the effects of alcohol, carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects; however, the concomitant use of sertraline and alcohol is not recommended.

Lithium

In placebo-controlled trials in normal volunteers, the co-administration of sertraline with lithium did not significantly alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When co-administering sertraline with medications, such as lithium, which may act via serotonergic mechanisms, patients should be appropriately monitored.

Phenytoin

A placebo-controlled trial in normal volunteers suggests that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, it is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels.

Sumatriptan

There have been rare post-marketing reports describing patients with weakness, hyper-reflexia, incoordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. If concomitant treatment with sertraline and sumatriptan is clinically warranted, appropriate observation of the patient is advised (see section 4.4 – **Special Warnings and Special Precautions for Use: Other Serotonergic Drugs**).

Other Serotonergic Drugs

Co-administration of sertraline with other drugs that enhance the effects of serotonergic neurotransmission, such as tryptophan, fenfluramine, and fentanyl, 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 pharmacodynamic interaction. (See section 4.4 – **Special Warnings and Special Precautions for Use**.)

Protein Bound Drugs

Since sertraline is bound to plasma proteins, the potential of sertraline to interact with other plasma protein bound drugs should be borne in mind. However, in three formal interaction studies with diazepam, tolbutamide and warfarin, respectively, sertraline was not shown to have significant effects on the protein binding of the substrate (see subsections Warfarin and Other Drug Interactions).

Warfarin

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

Other Drug Interactions

Formal drug interaction studies have been performed with sertraline. Co-administration of sertraline 200 mg daily with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters. Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction of sertraline 200 mg daily was observed with glibenclamide or digoxin.

Electroconvulsive Therapy

There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and sertraline.

Drugs Metabolized by Cytochrome P450 2D6

There is variability among antidepressants in the extent to which they inhibit the activity of isozyme cytochrome P450 (CYP) 2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered drug. CYP 2D6 substrates with a narrow therapeutic index include tricyclic antidepressants (TCAs) and class 1C antiarrhythmics, such as propafenone and flecainide. In formal interaction studies, chronic dosing with sertraline 50 mg daily showed minimal elevation (mean 23% to 37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isoenzyme activity).

Drugs Metabolized by Other CYP Enzymes (CYP 3A3/4, CYP 2C9, CYP 2C19, CYP 1A2)

CYP 3A3/4

In vivo interaction studies have demonstrated that chronic administration of sertraline 200 mg daily does not inhibit the CYP 3A3/4 mediated 6- β hydroxylation of endogenous cortisol or the metabolism of carbamazepine or terfenadine. In addition, the chronic administration of sertraline 50 mg daily does not inhibit the CYP 3A3/4 mediated metabolism of alprazolam. The data suggest that sertraline is not a clinically relevant inhibitor of CYP 3A3/4.

CYP 2C9

The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of tolbutamide, phenytoin and warfarin suggests that sertraline is not a clinically relevant inhibitor of CYP 2C9 (see subsections Other Drug Interactions, Phenytoin, and Warfarin).

CYP 2C19

The apparent lack of clinically significant effects of the chronic administration of sertraline 200 mg daily on plasma concentrations of diazepam suggests that sertraline is not a clinically relevant inhibitor of CYP 2C19 (see subsection Other Drug Interactions).

CYP 1A2

In vitro studies indicate that sertraline has little or no potential to inhibit CYP 1A2.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 times and 10 times the maximum daily human mg/kg dose, respectively. There was no evidence of teratogenicity at any dose level. At the dose level corresponding to approximately 2.5 to 10 times the maximum daily human mg/kg dose,

however, sertraline was associated with delayed ossification in fetuses, probably secondary to effects on the dams.

There was decreased neonatal survival following maternal administration of sertraline at doses approximately five times the maximum daily human mg/kg dose. Similar effects on neonatal survival have been described for other antidepressant drugs. The clinical significance of these effects is unknown.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sertraline should be used during pregnancy only if the perceived benefits outweigh the risks.

If sertraline is used during pregnancy and/or lactation, the physician should be aware of post-marketing reports of symptoms, including those compatible with withdrawal reactions, in some neonates whose mothers had been on SSRI antidepressants, including sertraline.

Women of child-bearing potential should employ an adequate method of contraception if taking sertraline.

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997 to 2005 found a PPHN risk ratio of 2.4 (95% CI, 1.2 to 4.3) associated with patient-reported maternal use of SSRIs “in early pregnancy” and a PPHN risk ratio of 3.6 (95% CI, 1.2 to 8.3) associated with a combination of patient-reported maternal use of SSRIs “in early pregnancy” and an antenatal SSRI prescription “in later pregnancy”.

Lactation

Isolated studies in small numbers of nursing mothers and their infants indicated negligible or undetectable levels of sertraline in infant serum, although levels in breast milk were more concentrated than in maternal serum. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefits outweigh the risks.

Fertility

There is no clinical trial data on fertility. In animal studies, no effect on fertility parameters was observed (see also section **5.3 - Preclinical safety data**).

4.7 Effects on Ability to Drive and Use Machines

Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However, as psychotropic drugs may impair the mental or physical abilities

required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, the patient should be cautioned accordingly.

4.8 Undesirable Effects

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

Adverse Reactions Table

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency not Known (cannot be estimated from the available data)
Blood and Lymphatic System Disorders				Leukopenia* [§] , thrombocytopenia* [§]	
Immune System Disorders			Hypersensitivity*	Anaphylactoid reaction*	
Endocrine Disorders			Hypothyroidism*	Inappropriate antidiuretic hormone secretion* [§] , hyperprolactinaemia* [§]	
Metabolism and Nutrition Disorders		Decreased appetite, increased appetite*		Diabetes mellitus*, hyponatraemia* [§] , hypoglycaemia* [§] , hyperglycaemia* [§]	
Psychiatric Disorders	Insomnia	Depressive symptoms*, libido decreased*, agitation*, anxiety*	Hallucination*, aggression*, euphoric mood*, confusional state*, bruxism*	Psychotic disorder* [§] , nightmare* [§]	
Nervous System Disorders	Somnolence, dizziness, headache*	Paraesthesia*, hypertonia*, tremor, muscle contractions involuntary*	Coma*, convulsions*, syncope*, extrapyramidal disorder*, hyperkinesia*, akathisia*, migraine*, hypoaesthesia*	Serotonin syndrome* [§] , dystonia* [§]	
Eye Disorders		Visual impairment*	Mydriasis*, periorbital oedema*		
Ear and Labyrinth Disorders		Tinnitus*			

Adverse Reactions Table

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency not Known (cannot be estimated from the available data)
Cardiac Disorders		Palpitations*	Tachycardia*	Torsade de Pointes*§	
Vascular Disorders		Hot flush*	Haemorrhage*, hypertension*	Cerebral vasoconstriction*§ (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome)	
Respiratory, Thoracic and Mediastinal Disorders		Yawning*	Bronchospasm*, epistaxis*		
Gastrointestinal Disorders	Diarrhoea, dry mouth, nausea	Vomiting*, abdominal pain*, constipation*, dyspepsia	Gastrointestinal haemorrhage*	Pancreatitis*§	
Hepatobiliary Disorders				Liver injury*§	
Skin and Subcutaneous Tissue Disorders		Rash*, Hyperhidrosis	Urticaria*, purpura*, pruritus*, alopecia*	Toxic epidermal necrolysis*§, Stevens-Johnson syndrome*§, angioedema*§, exfoliative rash*, photosensitivity skin reaction*§	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia*	Muscle spasms*	Trismus*§	rhabdomyolysis*§
Renal and Urinary Disorders			Urinary retention*, urinary incontinence*	Haematuria*, enuresis*§	
Reproductive System and Breast Disorders	Ejaculation disorder	Sexual dysfunction, menstruation irregular*		Priapism*, galactorrhoea*, gynaecomastia*§	
General Disorders and Administration Site	Fatigue*	Chest pain*, malaise*	Gait disturbance*, face oedema*, oedema peripheral*, pyrexia*, asthenia*	Drug withdrawal syndrome*§	

Adverse Reactions Table

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency not Known (cannot be estimated from the available data)
Conditions					
Investigations			Alanine aminotransferase increased*, aspartate aminotransferase increased*, Weight decreased*, weight increased*, Laboratory test abnormal*	Electrocardiogram QT prolonged*§, platelet function test abnormal*§, blood cholesterol increased*	
Injury, Poisoning and Procedural Complications				Fracture*	

* - ADR identified post-marketing

§ - ADR frequency estimated using “The Rule of 3/n”.

4.9 Overdose

Sertraline has a margin of safety dependent on patient population and/or concomitant medications. Deaths have been reported involving overdoses of sertraline, alone or in combination with other drugs and/or alcohol. Therefore, any overdose should be treated aggressively. Symptoms of overdose include serotonin-mediated side effects such as electrocardiogram QT prolonged, TdP, (see sections **4.4 - Special warnings and precautions, 4.5 - Interactions with other medicinal products and other forms of interaction and 5.1 – Pharmacodynamic properties**) somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness. Less frequently reported was coma.

There are no specific antidotes to sertraline. Establish and maintain an airway and ensure adequate oxygenation and ventilation, if necessary. Activated charcoal, which may be used with a cathartic, may be as or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended. Cardiac and vital sign monitoring is recommended, along with general symptomatic and supportive measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Sertraline is a potent and selective inhibitor of neuronal serotonin (5-HT) reuptake *in vitro*, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, gamma-aminobutyric acid (GABA) or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of brain norepinephrine receptors as observed with other clinically effective antidepressants and antiobsessional drugs.

Sertraline has not demonstrated potential for abuse. In a placebo-controlled, double-blind randomized study of the comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria and abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforcer in rhesus monkeys trained to self-administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

Clinical Trials

Major Depressive Disorder

A study was conducted that involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50 mg/day to 200 mg/day. These patients (N=295) were randomized to continuation for 44 weeks on double-blind sertraline 50 mg/day to 200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo. The mean dose for completers was 70 mg/day.

Obsessive-compulsive Disorder

In a long-term study, patients meeting DSM-III-R criteria for OCD who had responded during a 52-week single-blind trial on sertraline 50 mg/day to 200 mg/day (n=224) were randomized to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Patients receiving continued sertraline treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Panic Disorder

In a long-term study, patients meeting DSM-III-R criteria for panic disorder who had responded during a 52-week open trial on sertraline 50 mg/day to 200 mg/day (n=183) were randomized to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Patients receiving continued sertraline treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Post-traumatic Stress Disorder

In a long-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on sertraline 50 mg/day to 200 mg/day (n=96) were randomized to continuation of sertraline or to substitution of placebo for up to 28 weeks of observation for relapse. Patients receiving continued sertraline treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Social Phobia (Social Anxiety Disorder)

In a social phobia relapse prevention study, patients who were responders at the end of a 20 week, multicenter, flexible dose study that compared sertraline (50 mg/day to 200 mg/day) to placebo, were re-randomized for an additional 24 weeks to either sertraline continuation treatment (within 50 mg/day to 200 mg/day) or placebo substitution, while placebo responders remained on placebo. Patients receiving sertraline continuation treatment experienced a statistically significantly lower relapse rate over this 24-week study than patients randomized to placebo substitution treatment.

Cardiac Electrophysiology

In a dedicated thorough QTc study, conducted at steady-state at supratherapeutic 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 postdose time point. Exposure-response analysis indicated a slightly positive relationship between QTcF and sertraline plasma concentrations [0.036 msec/(ng/mL); p<0.0001]. Based on the exposure-response model, the threshold for clinically significant prolongation of the QTcF (i.e., for predicted 90% CI to exceed 10 msec) is at least 2.6-fold greater than the average C_{max} (86 ng/mL) following the highest recommended dose of sertraline (200 mg/day) (see sections **4.4 - Special warnings and precautions**, **4.5 - Interactions with other medicinal products and other forms of interaction**, **4.8 - Undesirable effects** and **4.9 - Overdose**).

Pre-menstrual Dysphoric Disorder (PMDD)

The effectiveness of sertraline for the treatment of PMDD was established in two double-blind, parallel group, placebo-controlled flexible dose trials (Studies 1 and 2) conducted over 3 menstrual cycles. Patients (n=251) in Study 1 met DSM-III-R criteria

for Late Luteal Phase Dysphoric Disorder (LLPDD), the clinical entity now referred to as Pre-menstrual Dysphoric Disorder (PMDD) in DSM-IV. Sertraline treatment was initiated at 50 mg/day and administered daily throughout the menstrual cycle. In subsequent cycles, patients were dosed in the range of 50-150 mg/day on the basis of clinical response and toleration. The mean dose for completers was 102 mg/day. Sertraline administered daily throughout the menstrual cycle was significantly more effective than placebo on change from baseline to endpoint on the Daily Record of Severity of Problems (DRSP) total score, the HAM-D-17 total score, and the CGI-S score, as well as the CGI-I score at endpoint. Patients in Study 2 (n=281) met DSM-IV criteria for PMDD. Sertraline treatment was initiated at 50 mg/day in the late luteal phase (last 2 weeks) of each menstrual cycle and then discontinued at the onset of menses. In subsequent cycles, patients were dosed in the range of 50-100 mg/day in the luteal phase of each cycle, on the basis of clinical response and toleration. Patients who were titrated to 100 mg/day received 50 mg/day for the first 3 days of the cycle, then 100 mg/day for the remainder of the cycle. The mean sertraline dose for completers was 74 mg/day. Sertraline administered in the late luteal phase of the menstrual cycle was significantly more effective than placebo on change from baseline to endpoint on the DRSP total score and the CGI-S score, as well as the CGI-I score at endpoint.

There was insufficient information to determine the effect of race or age on outcome in these studies.

5.2 Pharmacokinetic Properties

Sertraline exhibits dose-proportional pharmacokinetics over the range of 50 mg to 200 mg. In man, following oral once-daily dosing over the range of 50 mg to 200 mg for 14 days, peak plasma concentrations (C_{max}) of sertraline occur at about 4.5 to 8.4 hours post-dosing. The pharmacokinetic profile in either adolescents or the elderly is not significantly different from that in adults between 18 and 65 years. The mean half-life of sertraline for young and elderly men and women ranges from 22 to 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. Approximately 98% of the circulating drug is bound to plasma proteins. Animal studies indicate that sertraline has a large apparent volume of distribution. The pharmacokinetics of sertraline in pediatric OCD patients have been shown to be comparable to adults (although pediatric patients metabolize sertraline with slightly greater efficiency). However, lower doses may be advisable for pediatric patients, given their lower body weights (especially those patients aged 6 - 12 years), in order to avoid excessive plasma levels.

Sertraline undergoes extensive first-pass hepatic metabolism. The principal metabolite in plasma, N-desmethylsertraline, is substantially less active (about 20 times) than sertraline *in vitro*, and there is no evidence of activity in *in vivo* models of depression. The half-life of N-desmethylsertraline is in the range of 62 to 104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in feces and urine in equal amounts. Only a small amount (<0.2%) of unchanged sertraline is excreted in urine.

Food does not significantly change the bioavailability of sertraline tablets.

5.3 Preclinical Safety Data

Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective. Sertraline has also been shown to be devoid of mutagenic effects.

Juvenile Animal Studies

In a juvenile toxicology study in Sprague-Dawley rats, dose levels of 0, 10, 40 or 80 mg/kg/day of sertraline were administered orally to male and female rats on post-natal Days 21 through 56, with a non-dosing recovery phase up to post-natal Day 196. The administration of 80 mg/kg of sertraline to males and females on post-natal Days 21 to 56 resulted in dehydration, chromorrhinorrhea and reduced average body weight gain. In addition, rales, hunched posture and reduced food consumption also occurred in male rats given 80 mg/kg/day. Delays in sexual maturation occurred in males (80 mg/kg/day) and females (≥ 10 mg/kg/day), but despite this finding there were no sertraline-related effects on any of the male (organ weights, mating and fertility, sperm motility or sperm concentration) or female (estrous cycling, mating and fertility, or ovarian and uterine parameters) reproductive endpoints that were assessed. There were no sertraline-related effects on any behavior parameter (learning and memory, auditory startle response, and locomotor activity) in males, while a decrease in auditory startle response occurred in females at 40 and 80 mg/kg/day. There were no sertraline-related effects on male or female femur lengths, brain weights, gross necropsy or microscopic observations at any dose level. In juvenile males, the no-observed-adverse-effect level (NOAEL) for general toxicity was 40 mg/kg/day (correlating to a C_{max} of 262 ng/mL and an AUC_{0-t} of 3170 ng•h/mL on post-natal Day 56). In juvenile females, the NOAEL could not be established based on the delays in sexual maturation that occurred at ≥ 10 mg/kg. All of the aforementioned effects attributed to the administration of sertraline were reversed at some point during the non-dosing recovery phase of the study. The clinical relevance of these effects observed in rats administered sertraline has not been established.

Animal studies on fertility

In two studies conducted in rats, collective evidence did not show an effect on fertility parameters.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sertraline tablets 25 mg, 50 mg and 100 mg include the following inert ingredients:

Hydroxypropyl Cellulose I.P., Microcrystalline Cellulose I.P., Dibasic Calcium Phosphate dehydrate I.P., Sodium Starch Glycolate I.P., Magnesium Stearate I.P. and Purified water and

1] OPADRY (White) YS-1-7003 and 2] OPADRY (Clear) YS-1-7006.

1] OPADRY (White) is a patented and proprietary film coating composition provided by Colorcon Inc. and it contains the following composition:

Titanium Dioxide,
HPMC 2910/Hypromellose 3cP,
HPMC 2910/Hypromellose 6cP,
Macrogol/PEG 400,
Polysorbate 80.

2] OPADRY (Clear) is a patented and proprietary film coating composition provided by Colorcon Inc. and it contains the following composition:

HPMC 2910/Hypromellose 6cP,
Macrogol/PEG 8000,
Macrogol/PEG 400.

6.2 Incompatibilities

Not known

6.3 Shelf-life

36 months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and Contents of Container

2 strips of 15 tablets in Inner carton; 20 such inner carton in 1 outer carton.

6.6 Special Precautions for Disposal of a used Medicinal Product or Waste Materials Derived from such Medicinal Product and Other Handling of the Product

None