SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sertraline 50 mg Film-coated tablets
Sertraline 100 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Sertraline hydrochloride equivalent to 50 mg sertraline.

Each film coated tablet contains Sertraline hydrochloride equivalent to 100 mg sertraline.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet

White to off-white, caplet shaped, biconvex, film coated tablets with breakline on one side and "BL' and "50" debossed on either side of the breakline. The score line is not intended for breaking the tablets.

White to off-white, caplet shaped, biconvex, film coated tablets with 'BL' and '100' debossed on one side.

4 CLINICAL PROPERTIES

4.1. Therapeutic indications

Sertraline is indicated for the treatment of :

- Major depressive episodes. Prevention of recurrence of major depressive episodes.
- Panic disorder, with or without agoraphobia.
- Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years.
- Social anxiety disorder.
- Post traumatic stress disorder (PTSD).

4.2. Posology and method of administration

Posology

Initial treatment

Depression and OCD
Sertraline treatment should be started at a dose of 50 mg/day.

Panic Disorder, PTSD, and Social Anxiety Disorder:
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.

Titration:

Depression, OCD, Panic Disorder, Social Anxiety Disorder and PTSD
Patients not responding to a 50 mg dose may benefit from dose increases. Dose changes should be made in steps of 50 mg 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.

Maintenance:

Dosage during long-term therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response.

Depression:
Longer-term treatment may also be appropriate for prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during current episode. Patients with depression should be treated for a sufficient period of time of at least 6 months to ensure they are free from symptoms.

Panic disorder and OCD:
Continued treatment in panic disorder and OCD should be evaluated regularly, as relapse prevention has not been shown for these disorders.

Elderly patients:

Elderly should be dosed carefully, as elderly may be more at risk for hyponatraemia (see section 4.4).

Patients with hepatic impairment:
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). Sertraline should not be used in cases of severe hepatic impairment as no clinical data are available (see section 4.4).

Patients with renal impairment:
No dosage adjustment is necessary in patients with renal impairment (see section 4.4).

Paediatric population:

Children and adolescents with obsessive compulsive disorder
Age 13-17 years*:* Initially 50 mg once daily.
Age 6-12 years: Initially 25 mg once daily. The dosage may be increased to 50 mg once daily after one week.

Subsequent doses may be increased in case of less than desired response in 50 mg increments over a period of some weeks, as needed. The maximum dosage is 200 mg daily. 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. Dose changes should not occur at intervals of less than one week.

Efficacy is not shown in paediatric major depressive disorder.

No data is available for children under 6 years of age (see also section 4.4).

Method of administration:
Sertraline tablets are for oral administration only.
Sertraline should be administered once daily, either in the morning or evening.
Sertraline tablets can be administered with or without food.

Withdrawal symptoms seen on discontinuation of Sertraline Tablets
Abrupt discontinuation should be avoided. When stopping treatment with 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 and section 4.8). 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 the active substance or any of the excipients listed in section 6.1.

Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an

irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see section 4.5).

Concomitant intake of pimozide is contra-indicated (see section 4.5).

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 SSRIs, including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of other serotonergic drugs (including other serotonergic antidepressants, amphetamines, triptans), with drugs which impair metabolism of serotonin (including MAOIs e.g. methylene blue), antipsychotics and other dopamine antagonists, and with opiate drugs. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome (see section 4.3).

Switching from Selective Serotonin Reuptake Inhibitors (SSRIs), antidepressants or anti-obsessional drugs:
There is limited controlled experience regarding the optimal timing of switching from SSRIs, antidepressants or anti-obsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents such as fluoxetine.

Other serotonergic drugs e.g. tryptophan, fenfluramine and 5-HT agonists:
Co-administration of sertraline with other drugs which enhance the effects of serotonergic neurotransmission such as amphetamines, 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.

QTc Prolongation/Torsade de Pointes (TdP):
Cases of QTc prolongation and Torsade de Pointes (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. Effect on QTc prolongation was confirmed in a thorough QTc study in healthy volunteers, with a statistically significant positive exposure response relationship. Therefore, sertraline should be used with caution in patients with additional risk factors for QTc prolongation such as cardiac disease, hypokalaemia or hypomagnesemia, familial history of QTc prolongation, bradycardia and concomitant use of medications which prolong QTc interval (see sections 4.5 and 5.1).

Schizophrenia:
Psychotic symptoms might become aggravated in schizophrenic patients.

***Seizures*:**

Seizures may occur with sertraline therapy: Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be avoided in any patient who develops seizures.

***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 drugs, including sertraline. Therefore, sertraline should be used with caution in patients with a history of mania/hypomania. Close surveillance by the physician is required. Sertraline should be discontinued in any patient entering a manic phase.

***Suicide /suicidal thoughts/suicide attempts or clinical worsening*:**
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Sertraline is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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.

Paediatric population;

Sertraline should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with obsessive compulsive disorder aged 6-17 years old. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for appearance of suicidal symptoms, especially in early treatment. In addition only limited clinical evidence is available concerning, long-term safety data on cognitive, emotional, physical, and pubertal maturation in children and adolescents aged 6 to 16 years old was evaluated in a long term observational study for up to 3 years (see section 5.1). A few cases of retarded growth and delayed puberty have been reported post-marketing. The clinical relevance and causality are yet unclear (see section 5.3 for corresponding preclinical safety data). Physicians must monitor paediatric patients on long term treatment for abnormalities in growth and development.

Akathisia/Psychomotor restlessness:

The use of 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.

Hyponatraemia:

Hyponatraemia may occur as a result of treatment with SSRIs or SNRIs including 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 Use in elderly). Discontinuation of 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 have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Abnormal bleeding/Haemorrhage:

There have been reports of bleeding abnormalities with SSRIs including cutaneous bleeding (ecchymoses and purpura) and other haemorrhagic events such as gastrointestinal or gynaecological bleeding, including fatal haemorrhages. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. anticoagulants, atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders (see section 4.5).

Hepatic impairment:
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 Cmax 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 must be approached with caution. If sertraline is administered to patients with hepatic impairment, a lower or less frequent dose should be considered. Sertraline should not be used in patients with severe hepatic impairment (see section 4.2).

Renal impairment:
Sertraline is extensively metabolised, and 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 Cmax) were not significantly different compared with controls. Sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Use in the elderly:
Over 700 elderly patients (>65 years) have participated in clinical studies. The pattern and incidence of adverse reactions in the elderly was similar to that in younger patients.

SSRIs or SNRIs including 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 in section 4.4).

Diabetes:
In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Electroconvulsive therapy:
There are no clinical studies establishing the risks or benefits of the combined use of ECT and sertraline.

Grapefruit juice:
The administration of 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 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.

Withdrawal symptoms seen on discontinuation of Sertraline:
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, among patients treated with sertraline, the incidence of reported withdrawal reactions was 23% in those discontinuing sertraline compared to 12% in those who continued to receive sertraline treatment.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.
Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that Sertraline should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see Section 4.2).

Important information regarding the ingredients of this medicine

Sodium: This medicine contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated

Buprenorphine-containing medicinal products should be used cautiously when co-administered with:
Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Monoamine oxidase inhibitors

Irreversible MAOIs (e.g. selegiline):

Sertraline must not be used in combination with irreversible MAOIs such as selegiline. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see section 4.3).

Reversible, selective MAO-A inhibitor (moclobemide):
Due to the risk of serotonin syndrome, the combination of sertraline with a reversible and selective MAOI, such as moclobemide, should not be given. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of sertraline treatment. It is recommended that sertraline should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.3).

Reversible, non-selective MAOI (linezolid):
The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with sertraline (see section 4.3).

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI (e.g. methylene blue) and started on sertraline or have recently had sertraline therapy discontinued prior to initiation of an 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 levels of approximately 35% have been demonstrated in a study of a single low dose pimozide (2 mg). These increased levels were not associated with any changes in 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 (see section 4.3).

Co-administration with sertraline is not recommended

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.

Other serotonergic drugs
See section 4.4.
Caution is also advised with opioids [e.g. fentanyl (used in general anaesthesia or in the treatment of chronic pain)], and other serotonergic drugs (including other serotonergic antidepressants, amphetamines, triptans), and with other opiate drugs.

Special Precautions

Drugs that Prolong the QT Interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. TdP) may be increased with concomitant use of other drugs which prolong the QTc interval (e.g. some antipsychotics and antibiotics) (see sections 4.4 and 5.1).

Lithium
In a placebo-controlled trial 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 lithium, 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, as some case reports have emerged of high phenytoin exposure in patients using sertraline, 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, a known CYP3A4 inducer, may cause a reduction of 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 sertraline plasma levels.

Metamizole
Co-administration of sertraline with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4, may cause a reduction in plasma concentrations of sertraline with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and sertraline are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

Triptans
There have been rare post-marketing reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. Symptoms of serotonergic syndrome may also occur with other products of the same class (triptans). If concomitant treatment with sertraline and triptans is clinically warranted, appropriate observation of the patient is advised (see section 4.4).

Warfarin
Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time, which may in some rare cases unbalance the INR value.

Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Other drug interactions, digoxin, atenolol, cimetidine
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 digoxin.

Drugs affecting platelet function
The risk of bleeding may be increased when medicines acting on platelet function (e.g. NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might increase bleeding risk are concomitantly administered with SSRIs, including sertraline (see section 4.4).

Neuromuscular Blockers
SSRIs may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of mivacurium or other neuromuscular blockers.

Drugs Metabolized by Cytochrome P450
Sertraline may act as a mild-moderate inhibitor of CYP 2D6. Chronic dosing with sertraline 50 mg daily showed moderate elevation (mean 23%-37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isozyme activity). Clinical relevant interactions may occur with other CYP 2D6 substrates with a narrow therapeutic index like class 1C antiarrhythmics such as propafenone and flecainide, TCAs and typical antipsychotics, especially at higher sertraline dose levels.

Sertraline does not act as an inhibitor of CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2 to a clinically significant degree. This has been confirmed by in-vivo interaction studies with CYP3A4 substrates (endogenous cortisol, carbamazepine, terfenadine, alprazolam), CYP2C19 substrate diazepam, and CYP2C9 substrates tolbutamide, glibenclamide and phenytoin. *In vitro* studies indicate that sertraline has little or no potential to inhibit CYP 1A2.

Intake of three glasses of grapefruit juice daily increased the sertraline plasma levels by approximately 100% in a cross-over study in eight Japanese healthy subjects. Therefore, the intake of grapefruit juice should be avoided during treatment with sertraline (see section 4.4).

Based on the interaction study with grapefruit juice, it cannot be excluded that the concomitant administration of 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 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 sertraline.

It cannot be excluded that CYP3A4 inducers, e.g. phenobarbital, carbamazepine, St. John´s Wort and rifampicin, may cause a reduction of sertraline plasma levels.

Sertraline plasma levels are enhanced by about 50% in poor metabolizers of CYP2C19 compared to rapid metabolizers (see section 5.2). Interaction with

strong inhibitors of CYP2C19, e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole, fluoxetine, fluvoxamine cannot be excluded.

4.6. Fertility, pregnancy and lactation

Pregnancy:
There are no well controlled studies in pregnant women. However, a substantial amount of data did not reveal evidence of induction of congenital malformations by sertraline. Animal studies showed evidence for effects on reproduction probably due to maternal toxicity caused by the pharmacodynamic action of the compound and/or direct pharmacodynamic action of the compound on the foetus (see section 5.3).

Use of sertraline during pregnancy has been reported to cause symptoms, compatible with withdrawal reactions, in some neonates, whose mothers had been on sertraline. This phenomenon has also been observed with other SSRI antidepressants. Sertraline is not recommended in pregnancy, unless the clinical condition of the woman is such that the benefit of the treatment is expected to outweigh the potential risk.

Neonates should be observed if maternal use of sertraline continues into the later stages of pregnancy, particularly the third trimester. The following symptoms may occur in the neonate after maternal sertraline use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty in sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances, the complications begin immediately or soon (<24 hours*)* after delivery.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

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).

Breast-feeding:
Published data concerning sertraline levels in breast milk show that small quantities of sertraline and its metabolite N-desmethylsertraline are excreted in milk. Generally negligible to undetectable levels were found in infant serum, with one exception of an infant with serum levels about 50% of the maternal level (but without a noticeable health effect in this infant). To date, no adverse effects on the health of infants nursed by mothers using sertraline have been reported, but a risk cannot be excluded. Use in nursing mothers is not

recommended unless, in the judgment of the physician, the benefit outweighs the risk.

Fertility:
Animal data did not show an effect of sertraline on fertility parameters (see section 5.3).
Human case reports with some SSRIs have shown that an effect on sperm quality is reversible.
Impact on human fertility has not been observed so far.

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

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.

Table 1 displays adverse reactions observed from post-marketing experience (frequency not known) and placebo-controlled clinical trials (comprising a total of 2542 patients on sertraline and 2145 on placebo) in depression, OCD, panic disorder, PTSD and social anxiety disorder.

Some adverse drug reactions listed in Table 1 may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Table 1: Adverse Reactions
Frequency of adverse reactions observed from placebo-controlled clinical trials in depression, OCD, panic disorder, PTSD and social anxiety disorder. Pooled analysis and post-marketing experience.

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Frequency not Known (cannot be estimated**

				from the available data)
Infections and Infestations				
	Pharyngitis, Upper Respiratory Tract Infection, Rhinitis	Gastroenteritis, Otitis Media	Diverticulitis§,	
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
		Neoplasm		
Blood and lymphatic system disorders				
			Lymphadenopathy Leukopenia*§, Thrombocytopenia*§	
Immune system disorders				
		Hypersensitivity* Seasonal Allergy*	Anaphylactoid Reaction*	
Endocrine disorders				
		Hypothyroidism*	Hyper-prolactinaemia*§, inappropriate antidiuretic hormone secretion*§	
Metabolism and Nutrition Disorders				
	Decreased Appetite, Increased Appetite*		Diabetes mellitus*, Hyper-cholesterolaemia, Hypoglycaemia* Hyponatremia*§ Hyperglycaemia*§	
Psychiatric Disorders				
Insomnia	Depression*, Depersonalisation, Nightmare, Anxiety*, Agitation*, Nervousness, Libido decreased*, Bruxism*	Hallucination*, Aggression*, Euphoric Mood*, Apathy, Thinking Abnormal, Suicidal ideation/ behaviour, Psychotic disorder*, Paranoia	Conversion Disorder*§, Paroniria*§ Drug Dependence, Sleep Walking, Premature Ejaculation	
Nervous System Disorders				
Dizziness Somnolence Headache*	Paraesthesia*, Tremor, Movement Disorders	Convulsion*, Muscle Contractions Involuntary*,	Coma*, Akathisia (see section 4.4), Dyskinesia, Hyperaesthesia,	

	(including extrapyramidal symptoms such as hyperkinesia, hypertonia, dystonia, teeth grinding or gait abnormalities), Hypertonia*, Dysgeusia, Disturbance in Attention	Coordination Abnormal, Hyperkinesia*, Amnesia, Hypoaesthesia*, Speech Disorder, Dizziness Postural coordination abnormal, Syncope*, Migraine*	Sensory Disturbance Cerebrovascular Spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome) *§, psychomotor restlessness*§ (see section 4.4), sensory disturbance, choreoathetosis§, also reported were signs and symptoms associated with Serotonin Syndrome* or Neuroleptic Malignant Syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia§	
Eye Disorders				
	Visual Disturbance *	Mydriasis*	Glaucoma, Lacrimal Disorder, Scotoma, Diplopia, Photophobia, Hyphaema*§, Pupils Unequal*§, Vision Abnormal§	Maculopathy
Ear and Labyrinth Disorders				
	Tinnitus*	Ear Pain		
Cardiac Disorders				
	Palpitations*	Tachycardia* Cardiac Disorder	Myocardial Infarction*§, Bradycardia, Torsade de Pointes*§ (see section 4.4, 4.5 and 5.1), QTc prolongation* (see sections 4.4, 4.5 and 5.1)	

Vascular Disorders				
	Hot flush*	Hypertension*, Flushing Haematuria* Abnormal Bleeding (such as gastrointestinal bleeding) *	Peripheral Ischaemia,	
Respiratory, Thoracic, and Mediastinal Disorders				
	Yawning*	Bronchospasm*, Dyspnoea, Epistaxis*	Laryngospasm, Hyperventilation, Hypoventilation, Stridor*§, Dysphonia, Hiccups, Interstitial Lung Disease*§ eosinophilic pneumonia*§,	
Gastrointestinal Disorders				
Diarrhoea, Nausea, Dry Mouth	Abdominal Pain* Vomiting*, Constipation* Dyspepsia, Flatulence	Oesophagitis, Dysphagia, Haemorrhoids, Salivary Hypersecretion, Tongue Disorder, Eructation, Melaena, Tooth Disorder, Glossitis	Haematochezia, Stomatitis, Tongue ulceration, Mouth Ulceration Pancreatitis*§	Colitis microscopic*
Hepatobiliary Disorders				
			Hepatic Function Abnormal, Serious liver events (including hepatitis, jaundice and hepatic failure)	
Skin and Subcutaneous Tissue Disorders				
	Rash*, Hyperhidrosis	Periorbital Oedema*, Face Oedema, Purpura*, Dermatitis, Alopecia*, Cold Sweat, Dry skin, Urticaria*, Pruritus*	Rare reports of severe cutaneous adverse reactions (SCAR): e.g. Stevens-Johnson syndrome* and epidermal necrolysis*§ Skin Reaction*§ Angioedema, Photosensitivity§ Hair texture abnormal,	

			Skin odour abnormal, Dermatitis bullous, Rash follicular	
Musculoskeletal and Connective Tissue Disorders				
	Arthralgia*, Myalgia Back Pain	Osteoarthritis, Muscular Weakness, Muscle Twitching Muscle Cramps*	Bone Disorder Rhabdomyolysis*§	Trismus*, Multiple acyl-coenzyme A dehydrogenase deficiency (MADD)-like disorder*
Renal and Urinary Disorders				
		Nocturia, Urinary Retention, Polyuria, Pollakiuria, Micturition disorder, Urinary Incontinence*	Oliguria, Urinary Hesitation*	
Reproductive System and Breast Disorders*				
Ejaculation Failure	Erectile Dysfunction, Menstruation irregular*	Vaginal Haemorrhage, Sexual Dysfunction (see section 4.4), Female Sexual Dysfunction (see section 4.4), Menorrhagia	Atrophic Vulvovaginitis, Balanoposthitis*§, Genital Discharge, Priapism*, Galactorrhoea* Gynaecomastia*	Postpartum haemorrhage*†
General Disorders and Administration Site Conditions				
Fatigue *	Chest Pain*, Malaise* Asthenia* Pyrexia*	Oedema Peripheral*, Chills, Thirst, Gait Disturbance*	Hernia, Drug Tolerance Decreased,	
Investigations				
	Weight Increased*	Alanine Aminotransferase increased*, Aspartate Aminotransferase increased*, Weight decreased*,	Semen abnormal, Blood cholesterol increased*, Abnormal clinical laboratory results, Altered platelet function*§	
Injury and poisoning				
	Injury			
Surgical and medical procedures				

			Vasodilation procedure	

* ADR identified post-marketing
† This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).
§ADR frequency represented by the estimated upper limit of the 95% confidence interval using "The Rule of 3".

Withdrawal symptoms seen on discontinuation of sertraline treatment
Discontinuation of sertraline (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when sertraline treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Elderly population
SSRIs or SNRIs including sertraline have been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse event (see section 4.4).

Paediatric population
In over 600 paediatric patients treated with sertraline, the overall profile of adverse reactions was generally similar to that seen in adult studies. The following adverse reactions were reported from controlled trials (n=281 patients treated with sertraline):

***Very common (≥1/10)*:** Headache (22%), insomnia (21%), diarrhoea (11%) and nausea (15%).

***Common (≥1/100 to <1/10)*:** Chest pain, mania, pyrexia, vomiting, anorexia, affect lability, aggression, agitation, nervousness, disturbance in attention, dizziness, hyperkinesia, migraine, somnolence, tremor, visual disturbance, dry mouth, dyspepsia, nightmare, fatigue, urinary incontinence, rash, acne, epistaxis, flatulence.

***Uncommon (≥1/1000 to <1/100)*:** ECG QT prolonged (see sections 4.4, 4.5 and 5.1), suicide attempt, convulsion, extrapyramidal disorder, paraesthesia, depression, hallucination, purpura, hyperventilation, anaemia, hepatic function abnormal, alanine aminotransferase increased, cystitis, herpes simplex, otitis externa, ear pain, eye pain, mydriasis, malaise, haematuria, rash pustular, rhinitis, injury, weight decreased, muscle twitching, abnormal dreams, apathy, albuminuria, pollakiuria, polyuria, breast pain, menstrual disorder, alopecia, dermatitis, skin disorder, skin odour abnormal, urticaria, bruxism, flushing.

***Frequency not known*:** enuresis

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Toxicity

Sertraline has a margin of safety dependent on patient population and/or concomitant medication. Deaths have been reported involving overdoses of Sertraline, alone or in combination with other drugs and/or alcohol. Therefore, any overdosage should be treated aggressively.

Symptoms

Symptoms of overdose include serotonin-mediated side effects such as somnolence, gastrointestinal disturbances (e.g. nausea and vomiting), tachycardia, tremor, agitation and dizziness. Coma has been reported although less frequently.

QTc prolongation/Torsade de Pointes has been reported following sertraline overdose; therefore, ECG-monitoring is recommended in all ingestions of sertraline overdoses (see sections 4.4, 4.5 and 5.1).

Management

There are no specific antidotes to Sertraline. It is recommended to establish and maintain an airway and if necessary, 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 (e.g. ECG) 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, 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

Mechanism of action

Sertraline is a potent and specific inhibitor of neuronal serotonin (5 HT) uptake 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, 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 efficacy and safety

Major Depressive Disorder
A study was conducted which involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50-200 mg/day. These patients (n=295) were randomized to continuation for 44 weeks on double-blind sertraline 50-200 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. The % of responders (defined as those patients that did not relapse) for sertraline and placebo arms were 83.4% and 60.8%, respectively.

Post traumatic stress disorder (PTSD)
Combined data from the 3 studies of PTSD in the general population found a lower response rate in males compared to females. In the two positive general population trials, the male and female sertraline vs. placebo responder rates were similar (females: 57.2% vs 34.5%; males: 53.9% vs 38.2%). The number of male and female patients in the pooled general population trials was 184 and 430, respectively and hence the results in females are more robust and males were associated with other baseline variables (more substance abuse, longer duration, source of trauma etc) which are correlated with decreased effect.

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 Cmax (86 ng/mL) following the highest recommended dose of sertraline (200 mg/day) (see sections 4.4, 4.5, 4.8 and 4.9).

Paediatric OCD

The safety and efficacy of sertraline (50-200 mg/day) was examined in the treatment of non-depressed children (6-12 years old) and adolescent (13-17 years old) outpatients with obsessive compulsive disorder (OCD). After a one week single blind placebo lead-in, patients were randomly assigned to twelve weeks of flexible dose treatment with either sertraline or placebo. Children (6-12 years old) were initially started on a 25 mg dose. Patients randomized to sertraline showed significantly greater improvement than those randomised to placebo on the Children's Yale-Brown Obsessive Compulsive Scale CY-BOCS (p =0.005) the NIMH Global Obsessive Compulsive Scale (p=0.019), and the CGI Improvement (p =0.002) scales. In addition, a trend toward greater improvement in the sertraline group than the placebo group was also observed on the CGI Severity scale (p=0.089). For CY-BOCs the mean baseline and change from baseline scores for the placebo group was 22.25 ± 6.15 and -3.4 ± 0.82, respectively, while for the sertraline group, the mean baseline and change from baseline scores were 23.36 ± 4.56 and -6.8 ± 0.87, respectively. In a post-hoc analysis, responders, defined as patients with a 25% or greater decrease in the CY-BOCs (the primary efficacy measure) from baseline to endpoint, were 53% of sertraline-treated patients compared to 37% of placebo-treated patients (p=0.03).

Long term safety and efficacy data are lacking for this paediatric population.

Paediatric population

No data is available for children under 6 years of age.

Post-marketing safety study SPRITES

An observational post-approval study of 941 patients aged 6 to 16 years old was conducted to evaluate the long-term safety of treatment with sertraline (with and without psychotherapy) compared with psychotherapy on cognitive, emotional, physical, and pubertal maturation for up to 3 years. This study was conducted in clinical practice settings in children and adolescents with primary diagnoses of obsessive compulsive disorder, depression, or other anxiety disorders and evaluated cognition [assessed by the Trails B test and the Metacognition Index from the Behaviour Rating Inventory of Executive Function (BRIEF), behavioural/emotional regulation (assessed by the Behavioural Regulation Index from the BRIEF) and physical/pubertal maturation (assessed by

standardized height/weight/body mass index (BMI) and Tanner Stage)]. Sertraline is approved in the paediatric population only for patients aged 6 years of age and older with OCD (see section 4.1).

Standardization of each primary outcome measure based on sex and age norms showed that the overall results were consistent with normal development. No statistically significant differences were observed for the primary outcome measures, with the exception of weight. A statistically significant finding for standardized weight was observed in comparative analyses; however, the magnitude of the change in weight was small [mean (SD) change in standardized z-scores <0.5 SD]. There was a dose-response relationship in weight gain.

5.2 Pharmacokinetic properties

Absorption
Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200mg. In man, 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 of the drug. Food does not significantly change the bioavailability of sertraline tablets.

Distribution
Approximately 98% of the circulating drug 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 metabolized by multiple pathways including CYP3A4, CYP2C19 (see section 4.5) and CYP2B6. Sertraline and its major metabolite desmethylsertraline are also substrate of P-glycoprotein *in-vitro*.

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 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 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.

Pharmacokinetics in specific patient groups

Paediatric patients with OCD

Pharmacokinetics of sertraline was studied in 29 paediatric patients aged 6-12 years old, and 32 adolescent patients aged 13-17 years old. Patients were gradual uptitrated to a 200 mg daily dose within 32 days, either with 25 mg starting dose and increment steps, or with 50 mg starting dose or increments. The 25 mg regimen and the 50 mg regimen were equally tolerated. In steady state for the 200 mg dose, the sertraline plasma levels in the 6-12 year old group were approximately 35% higher compared to the 13-17 year old group, and 21% higher compared to adult reference group. There were no significant differences between boys and girls regarding clearance. A low starting dose and titration steps of 25 mg are therefore recommended for children, especially with low bodyweight. Adolescents could be dosed like adults.

Adolescents and elderly
The pharmacokinetic profile in adolescents or elderly is not significantly different from that in adults between 18 and 65 years.

Liver function 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.

Pharmacogenomics
Plasma levels of sertraline were about 50% higher in poor metabolizers of CYP2C19 versus extensive metabolizers. The clinical meaning is not clear, and patients need to be titrated based on clinical response.

5.3 Preclinical safety data

Preclinical data does not indicate any special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenesis. Reproduction toxicity studies in animals showed no evidence of teratogenicity or adverse effects on male fertility. Observed foetotoxicity was probably related to maternal toxicity. Postnatal pup survival and body weight were decreased only during the first days after birth. Evidence was found that the early postnatal mortality was due to in-utero exposure after day 15 of pregnancy. Postnatal developmental delays found in pups from treated dams were probably due to effects on the dams and therefore not relevant for human risk.

Animal data from rodents and non-rodents does not reveal effects on fertility.
Juvenile animal studies
A juvenile toxicology study in rats has been conducted in which sertraline was administered orally to male and female rats on Postnatal Days 21 through 56 (at doses of 10, 40, or 80 mg/kg/day) with a nondosing recovery phase up to Postnatal Day 196. Delays in sexual maturation occurred in males and females at different dose levels (males at 80 mg/kg and females at ≥10 mg/kg), but

despite this finding there were no sertraline-related effects on any of the male or female reproductive endpoints that were assessed. In addition, on Postnatal Days 21 to 56, dehydration, chromorhinorrhea, and reduced average body weight gain was also observed. All of the aforementioned effects attributed to the administration of sertraline were reversed at some point during the nondosing recovery phase of the study. The clinical relevance of these effects observed in rats administered sertraline has not been established.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium hydrogen phosphate
Microcrystalline cellulose
Hydroxypropylcellulose
Sodium starch glycolate (Type A)
Magnesium stearate
Hypromellose
Macrogol 400
Titanium dioxide (E 171)
Polysorbate – 80

6.2. Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4. Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

Al/PVC blister, pack sizes of 28 or 56 tablets.
Not all pack sizes may be marketed.

6.6. Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road,
Berkhamsted, Herts, HP4 1EG
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 17907/0087
PL 17907/0088

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/10/2005

10 DATE OF REVISION OF THE TEXT

22/10/2026