IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0408/059/002
Case No: 2088079

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Ranbaxy Ireland Limited

Spafield, Cork Road, **Cashel**, **Co. Tipperary**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Sertraline Ranbaxy 100 mg Film-coated Tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **23/08/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sertraline 100 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 100 mg of sertraline as sertraline hydrochloride.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White film-coated caplet shaped tablet embossed with “100” on one side and break-line on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sertraline is indicated for the treatment of:
Major depressive episodes

4.2 Posology and method of administration

Sertraline should be taken once daily, either in the morning or evening
Sertraline tablet can be administered with or without food.

Initial treatment
Adults:
Sertraline treatment should be started at a dose of 50 mg / day.

Titration
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.

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

Patients with depression should be treated for a sufficient period of time of at least 6 months to ensure they are free from symptoms.

Children and adolescents
Sertraline is not recommended for treatment of major depressive episodes in children and adolescents under 18 years of age as safety and efficacy have not been established in this population.

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

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

Use in renal insufficiency
No dosage adjustment is necessary in patients with renal insufficiency (see section 4.4).

Withdrawal symptoms seen on discontinuation of sertraline
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 sections 4.4 and 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.
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 contraindicated (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 serotonergic drugs (including triptans), with drugs which impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. 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 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.

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 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.

Activation of hypomania or mania
Manic/ hypomanic symptoms have been reported to emerge in a small proportion of patients treated with marketed antidepressant and antiobsessional 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.

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 discontinued in any patient who develops

seizures.

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.

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.

Use in children and adolescents under 18 years of age
Sertraline should not be used in the treatment of children and adolescents under the age of 18 years 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 the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Abnormal bleeding / Haemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura and other hemorrhagic events such as gastrointestinal or gynaecological bleeding, with SSRIs. 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-steroids anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders (see section 4.5.)

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.

Withdrawal symptoms seen on discontinuation of sertraline treatment
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).

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.

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 was 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 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, possibly due to improvement of depressive symptoms. Glycaemic control should be carefully monitored in patients receiving sertraline and the dosage of insulin and/or concomitant oral hypoglycaemic medicinal products may be needed to be adjusted.

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

4.5 Interaction with other medicinal products and other forms of interaction

<u>Contraindicated</u>
Monoamine Oxidase Inhibitors
Irreversible (non-selective) MAOIs (selegiline)
Sertraline must not be used in combination with irreversible (non-selective) MAOIs such as selegiline. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible (non-selective) MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible (non-selective) 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, is not recommended. 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 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

Special Precautions
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 may cause a reduction of plasma Sertraline levels.

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 200mg 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 200mg 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).

Drugs metabolized by Cytochrome P450
Sertraline may act as a mild-moderate inhibitor of CYP 2D6. Chronic dosing with Sertraline 50mg daily showed moderate elevation (mean 23%-37%) of steady state desipramine plasma levels (a marker of CYP2D6 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.

4.6 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 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.

Breastfeeding
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.

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.

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 (frequency not known).

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
Infections and Infestations					
	Pharyngitis	Upper Respiratory Tract Infection, Rhinitis	Diverticulitis, Gastroenteritis, Otitis Media		
Neoplasms benign, malignant (including cysts and polyps)					
			Neoplasm†		
Blood and lymphatic system disorders					
			Lymphadenopathy		Leucopenia, Thrombocytopenia
Immune system disorders					
					Anaphylactoid Reaction, Allergic Reaction, Allergy
Endocrine disorders					
					Hyperprolactinaemia, Hypothyroidism and syndrome of inappropriate ADH secretion
Metabolism and Nutrition Disorders					
	Anorexia, Increased Appetite*		Hypercholesterolaemia, Hypoglycaemia		Hyponatraemia
Psychiatric Disorders					
Insomnia (19%)	Depression*, Depersonalisation, Nightmare, Anxiety*, Agitation*, Nervousness, Libido Decreased*, Bruxism	Hallucination*, Euphoric Mood*, Apathy, Thinking Abnormal	Conversion Disorder, Drug Dependence, Psychotic disorder*, Aggression*, Paranoia, Suicidal Ideation, Sleep Walking, Premature Ejaculation		Paroniria, Suicidal ideation/behaviour***
Nervous System Disorders					
Dizziness (11%), Somnolence (13%), Headache (21%) *	Paraesthesia*, Tremor, Hypertonia, Dysgeusia, Disturbance in Attention,	Convulsion*, Muscle Contractions Involuntary*, Coordination Abnormal, Hyperkinesia, Amnesia, Hypoaesthesia*, Speech Disorder, Dizziness Postural, Migraine*	Coma*, Choreoathetosis, Dyskinesia, Hyperaesthesia, Sensory Disturbance		Movement Disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, teeth grinding or gait abnormalities), Syncope. 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. Akathesia and pyschomotor restlessness (see section 4.4).
Eye Disorders					
	Visual Disturbance		Glaucoma, Lacrimal Disorder, Scotoma, Diplopia, Photophobia, Hyphaema, Mydriasis*		Vision Abnormal
Ear and Labyrinth Disorders					
	Tinnitus*	Ear Pain			
Cardiac Disorders					
	Palpitations*	Tachycardia	Myocardial Infarction, Bradycardia, Cardiac Disorder		
Vascular Disorders					
	Hot flush*	Hypertension*, Flushing	Peripheral Ischaemia		Abnormal Bleeding (such as epistaxis, gastrointestinal bleeding or haematuria)
Respiratory, Thoracic, and Mediastinal Disorders					
	Yawning*	Bronchospasm*, Dyspnoea, Epistaxis	Laryngospasm, Hyperventilation, Hypoventilation, Stridor, Dysphonia, Hiccups		
Gastrointestinal Disorders					
Diarrhoea (18%), Nausea (24%), Dry Mouth (14%)	Abdominal Pain* Vomiting*, Constipation* Dyspepsia, Flatulence	Oesophagitis, Dysphagia, Haemorrhoids, Salivary Hypersecretion, Tongue Disorder, Eructation	Melaena, Haematochezia, Stomatitis, Tongue ulceration, Tooth Disorder, Glossitis, Mouth Ulceration		Pancreatitis
Hepatobiliary Disorders					
			Hepatic Function Abnormal		Serious liver events (including hepatitis, jaundice and liver failure)
Skin and Subcutaneous Tissue Disorders					
	Rash*, Hyperhidrosis	Periorbital Oedema*, Purpura*, Alopecia*, Cold Sweat, Dry skin, Urticaria*	Dermatitis, Dermatitis Bullous, Rash Follicular, Hair Texture Abnormal, Skin Odour Abnormal		Rare reports of severe cutaneous adverse reactions (SCAR): e.g. Stevens-Johnson syndrome and epidermal necrolysis, Angioedema, Face Oedema, Photosensitivity, Skin Reaction, Pruritus
Musculoskeletal and Connective Tissue Disorders					
	Myalgia	Osteoarthritis, Muscular Weakness, Back Pain, Muscle Twitching	Bone Disorder		Arthralgia, Muscle Cramps, Bone fractures****
Renal and Urinary Disorders					
		Nocturia, Urinary Retention*, Polyuria,	Oliguria, Urinary Incontinence*, Urinary Hesitation		Enuresis

		Pollakiura, Micturition disorder			
*Reproductive System and Breast Disorders***					
Ejaculation Failure (14%)	Sexual Dysfunction, Erectile Dysfunction	Vaginal Haemorrhage, Female Sexual Dysfunction	Menorrhagia, Atrophic Vulvuvaginitis, Balanoposthitis, Genital Discharge, Priapism*, Galactorrhoea*		Gynaecomastia, Menstrual Irregularities
General Disorders and Administration Site Conditions					
Fatigue (10%)*	Chest Pain*	Malaise*, Chills, Pyrexia*, Asthenia*,Thirst	Hernia, Injection Site Fibrosis, Drug Tolerance Decreased, Gait Disturbance, Unevaluable Event		Oedema Peripheral
Investigations					
		Weight Decreased*, Weight Increased*	Alanine Aminotransferase Increased*, Aspartate Aminotransferase Increased*, Semen Abnormal		Abnormal Clinical Laboratory Results, Altered Platelet Function, Increased Serum Cholesterol
Injury and poisoning					
			Injury		
Surgical and medical procedures					
			Vasodilation Procedure		

If adverse experience occurred in depression body term reclassified by depression studies body term.

† One case of neoplasm was reported in one patient receiving sertraline compared with no cases in the placebo arm.

** these adverse reactions also occurred in post-marketing experience*

*** the denominator uses the number of patients in that sex group-combined: sertraline (1118 males, 1424 females) placebo (926 males, 1219 females)*

**** Cases of suicidal ideation and suicidal behaviours have been reported during sertraline therapy or early after treatment discontinuation (see section 4.4).*

*****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.*

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, 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).

4.9 Overdose

Toxicity
On the evidence available, Sertraline has a wide margin of safety in overdose. Overdoses of sertraline alone of up to 13.5 g have been reported. Deaths have been reported involving overdoses of sertraline, primarily in combination with other medications and/or alcohol. Therefore, any overdosage should be medically treated aggressively.

Symptoms
Symptoms of overdose include serotonin-mediated side-effects such as somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness. Less frequently reported was coma.

Treatment
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 other 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: N06AB06

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 Trials
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.

5.2 Pharmacokinetic properties

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

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.

Pharmacokinetics in specific patient groups
Elderly:
The pharmacokinetic profile of sertraline in elderly patients 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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline Cellulose
Calcium Hydrogen Phosphate Dihydrate
Sodium Starch Glycolate (type A)
Hydroxypropylcellulose
Magnesium Stearate

Tablet coat:
Hypromellose
Titanium Dioxide (E 171)
Macrogol
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 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

Blister pack comprising of white opaque PVC-film coated with PVdC on inner side with a backing of aluminium foil coated with heat seal lacquer.
Pack containing 20, 28, 30, 50, 98 or 100 film-coated tablets.
Hospital pack: 10 packs containing 30 film-coated tablets
Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy Ireland Limited
Spafield
Cork Road
Cashel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 0408/059/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 2006
Date of last renewal: 28 January 2008

10 DATE OF REVISION OF THE TEXT

August 2010