IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0711/084/002
Case No: 2032408

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

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

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

Sertraline 100 Milligram Film Coated Tablet

The particulars of which are set out in Part I and Part II of 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 **19/02/2007** until .

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sertraline 100mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 100mg Sertraline (as hydrochloride).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White, capsule shaped, film-coated, scored tablets coded `SE/100` on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of symptoms of depression, including accompanying symptoms of anxiety. Following satisfactory response, continuation with sertraline therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes, including accompanying symptoms of anxiety.

Sertraline is also indicated for the treatment of obsessive compulsive disorder (OCD). Following initial response, sertraline has been associated with sustained efficacy, safety and tolerability in up to two years treatment of OCD.

Sertraline is also indicated for the treatment of panic disorder, with or without agoraphobia.

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

Sertraline is also indicated for the treatment of post-traumatic stress disorder (PTSD).

Sertraline is indicated for the treatment of paediatric patients with OCD, aged 6 years and over.

4.2 Posology and method of administration

Adults
Sertraline tablets should be given as a single daily dose.

The starting dose in depression and OCD is 50 mg daily and the usual therapeutic dose for depression is 50 mg daily.

For OCD and panic disorder, the minimum recommended effective dose is 50 mg daily. However, therapy for panic disorder, social phobia and PTSD should commence at 25 mg daily, increasing to 50 mg daily after one week. This dosage regimen has been demonstrated to reduce the frequency of early treatment-emergent side-effects characteristic of panic disorder.

Because Social Phobia is a chronic illness, Sertraline can be taken for many weeks and dosing should be reviewed periodically to re-evaluate the long-term usefulness of the drug of the individual patient. A maximum of 44 weeks is represented in clinical trials.

The daily dose for all indications may be increased in 50 mg increments over a period of weeks. The maximum recommended dose of sertraline is 200 mg daily. 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, although 2-4 weeks (and even longer in OCD, social phobia and PTSD) are usually necessary for full activity.

Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level. Dosage during prolonged maintenance therapy should be kept at the lowest effective level, with subsequent adjustments depending on therapeutic response.

Use in children and adolescents with obsessive compulsive disorder (ages 6-17 years)
Sertraline tablets should be given as a single daily dose.

Treatment should be initiated by specialists.

The safety and efficacy of sertraline in paediatric OCD patients (aged 6 to 17). The administration of sertraline to paediatric OCD patients (aged 13-17) should commence at 50 mg/day. Therapy for paediatric OCD patients (aged 6-12) should commence at 25 mg/day increasing to 50 mg/day after 1 week. Paediatric patients not responding to 50 mg/day may benefit from dose increases, in 50 mg/day increments up to a maximum of 200 mg/day, with each dose increase occurring no sooner than one week after the last. However, the generally lower body weights of children compared to adults should be taken into consideration in advancing the dose from 50 mg, in order to avoid excessive dosing. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week.

Response to treatment should be considered when reviewing the patient's dosing regimen.

Use in children and adolescents under the age of 18 years with major depressive disorder is not recommended (see section 4.4).

Children aged less than 6 years – Sertraline is not recommended in children under 6 years of age since safety and efficacy have not yet been established.

Use in the elderly
No special precautions are required. The usual adult dosage is recommended. Several hundred elderly patients have participated in clinical studies with sertraline. The pattern and incidence of adverse reactions in the elderly was similar to that in younger patients.

Use in patients with renal insufficiency
No changes in dosage regimen for patients with renal impairment (not requiring dialysis) are recommended but renal function should be monitored regularly during treatment, especially in elderly patients.

4.3 Contraindications

Use in patients hypersensitive to this group of drugs. Use in conjunction with monoamine oxidase inhibitors (MAOIs) or use within 14 days of discontinuing these drugs.

Use in patients with unstable epilepsy or convulsant disorders.

Use in pregnancy and lactation.

Use in patients with significant hepatic dysfunction.

Concomitant use in patients taking pimozide is contraindicated. (See section 4.5- Interactions with other medicines and other forms of interaction).

4.4 Special warnings and precautions for use

Monoamine Oxidase Inhibitors – Cases of serious reactions, sometimes fatal, have been reported in patients receiving sertraline in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI, selegiline and the reversible MAOI moclobemide.

Some cases presented with features resembling the serotonin syndrome. Similar cases, sometimes fatal, have been reported with other antidepressants during combined treatment with a MAOI and in patients who have recently discontinued an antidepressant or anti-obsessional drug and have been started on a MAOI. Symptoms of a drug interaction between a selective serotonin re-uptake inhibitor (SSRI) and a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. Therefore, sertraline should not be used in combination with a MAOI or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should elapse after discontinuing Sertraline treatment before starting a MAOI.

Other Serotonergic drugs – Co-administration of sertraline with other drugs which enhance serotonergic neurotransmission, such as tryptophan or fenfluramine, should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction.

Switching from Other Antidepressants or Anti-obsessional Drugs – There is limited controlled experience regarding the optimal timing of switching from other 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. The duration of washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Suicide– As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved and its general clinical experience with antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

Because of the well-established comorbidity between OCD and depression and between PTSD and depression the same precautions observed when treating patients with depression should be observed when treating patients with OCD or PTSD.

Activation of mania/hypomania – Should the patient enter a manic phase, sertraline should be discontinued and appropriate treatment with a neuroleptic should be instituted.

Patients with hepatic impairment – Sertraline is extensively metabolized by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and approximately 3-fold greater AUC and C_{max} in comparison to normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of Sertraline in patients with significant hepatic disease is contra-indicated.

Patients with renal impairment – Sertraline is extensively metabolised, 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.

A multiple dose pharmacokinetic study showed no significant changes in pharmacokinetic parameters of sertraline in patients with mild, moderate or severe renal impairment compared to age and weight-matched control subjects. Half-lives were similar and there were no differences in plasma protein binding in all groups studied. No changes in dosage regimen for patients with renal impairment (not requiring dialysis) are recommended, but renal function should be monitored regularly during treatment especially in elderly patients.

Convulsions – Convulsions are a potential risk with antidepressant and anti-obsessional drugs. Convulsion was observed in three patients among approximately 4000 (approximately 0.08%) treated with sertraline in the development

program for depression. Four patients out of approximately 1800 exposed during the development program for OCD (approximately 0.2%) experienced convulsions. Three of these patients were adolescents, two with a convulsion disorder and one with a family history of convulsion disorder, none of whom were receiving anticonvulsant medication. In all these cases, the relationship to sertraline therapy was uncertain. Patients with controlled epilepsy should be carefully monitored. The drug should be discontinued in any patient who develops convulsions.

ECT (Electro-Convulsive Therapy) – Due to lack of experience in patients receiving ECT, concomitant administration of sertraline is not recommended.

Use in Children and adolescents under the age of 18 years – More than 250 paediatric OCD patients have been exposed to sertraline in completed and ongoing studies. The safety profile of sertraline in these paediatric studies are comparable to that observed in the adult OCD studies. The efficacy of sertraline in paediatric patients with depression or panic has not been demonstrated in controlled trials. Safety and effectiveness in paediatric patients below the age of 6 have not been established.

Sertraline should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder.

St John's Wort – Undesirable effects may be more common during concomitant use of serotonin re-uptake inhibitors and herbal preparations containing St John's Wort *(Hypericum Perforatum)*.

Haemorrhage – There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with SSRIs. Ecchymosis has been reported as an infrequent event during treatment with sertraline. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastro-intestinal bleedings, and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulant, drugs known to affect platelet function (e.g. atypical antipsychotics, such as clozapine, phenothiazines, most TCAs, aspirin, NSAIDs), or other drugs that may increase the risk of bleeding, as well as in patients with a history of bleeding disorders.

Use in children and adolescents under 18 years of age
Sertraline 50mg Film-coated Tablets should not be used in the treatment of children and adolescents under the age of 18 years except for patients with OCD. 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 patients 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.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase inhibitors – See Special Warnings and Special Precautions for Use.

Centrally active medication: Caution is advised if the concomitant administration of sertraline and other centrally active medication is required.

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

In placebo-controlled trials in normal volunteers, the co-administration of sertraline and lithium did not significantly alter lithium pharmacokinetics however it is recommended that plasma lithium levels be monitored following initiation of lithium therapy.

Co-administration of sertraline with lithium did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. As with other SSRI's, caution is recommended when co-administering sertraline with medications, such as lithium, which may act via serotonergic mechanisms and may lead to a higher incidence of 5-HT

associated side effects.

Other serotonergic drugs – See Special Warnings and Special Precautions for use.

Formal drug interaction studies have been performed with sertraline.

Co-administration of sertraline 200mg daily with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters.

Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction of sertraline 200mg daily was observed with glibenclamide or digoxin.

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

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

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

Sumatriptan: There have been reports describing patients with weakness, hyperreflexia, in-coordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. If concomitant treatment with sertraline and sumatriptan is clinically warranted, appropriate observation of the patient is advised. (See section 4.4 Special Warning and Precautions for Use: Other Serotonergic Drugs).

Tricyclic Antidepressants: Concurrent use of some tricyclic antidepressant (TCADs) may increase the plasma concentrations of selective serotonin re-uptake inhibitiors (SSRIs) to toxic levels.

4.6 Pregnancy and lactation

Use in pregnancy: The use of sertraline is contra-indicated during pregnancy. Women of child bearing potential should employ an adequate method of contraception if taking sertraline.

Use during lactation: Limited data concerning sertraline levels in breast milk are available hence use in nursing mothers is contra-indicated. Isolated studies in very small numbers of nursing mothers indicated variable amounts of sertraline and/or its metabolite were excreted in breast milk. Where levels were detectable in breast milk, they were less than one tenth maternal serum concentrations.

If sertraline is used during pregnancy and/ or lactation, physicians should be aware that symptoms including these compatible with withdrawal reactions have been reported in some neonates whose mothers had been on SSRI antidepressants, including sertraline.

4.7 Effects on ability to drive and use machines

Clinical studies have shown that sertraline has no effect on psychomotor performance. However, as drugs used to treat depression, OCD, panic or PTSD may impair the ability to perform potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly. Sertraline should not be administered with benzodiazepines or other tranquillisers in patients who drive or operate machinery.

4.8 Undesirable effects

Clinical Trial Data
Side effects that occurred significantly more frequently with sertraline than with placebo in multiple-dose studies for depression were:

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Insomnia.

Nervous System Disorders: Dizziness, somnolence and tremor.

Gastrointestinal Disorders: Diarrhoea/loose stools, dry mouth, dyspepsia and nausea.

Skin and Subcutaneous Tissues Disorders: Increased sweating.

Reproductive System and Breast Disorders: Sexual dysfunction (principally ejaculatory delay in males).

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

The overall safety profile is similar between adults and children.

Children and Adolescents with OCD
The following adverse events were observed in clinical trials in children and adolescents (aged 6 – 17 years old) with OCD and occurred at a frequency of at least 2% and at least twice that of placebo:

Anorexia (12% vs 4.2%), Weight decrease (2.2% vs 0%), Fatigue (5.4% vs 2.1%), Chest pain (4.3% vs 1.1%), Fever (3.3% vs 0%), Malaise (2.2% vs 0%), Hyperkinesia (8.7% vs 4.2%), Tremor (4.3% vs 0%), Urinary incontinence (3.3% vs 0%), Nausea (16.3% vs 5.3%), Insomnia (37% vs 11.6%), Nervousness (15.2% vs 5.3%), Agitation (13% vs 2.1%), Impaired concentration (3.3% vs 0%), Manic reaction (3.3% vs 0%), Anxiety (2.2% vs 1.1%), Emotional lability (2.2% vs 1.1%), Abnormal thinking (2.2% vs 0%), Breast pain (2.5% vs 0%), Dysmenorrhea (2.5% vs 0%), Menstrual Disorder (2.5% vs 0%), Epistaxis (2.2% vs 0%), Rash (4.3% vs 1.1%), Skin Disorder (2.2% vs 0%) and Purpura (2.2% vs 0%).

The incidence of headache in children (6 to 11 year olds) was 31.6% with sertraline versus 15% with placebo. The incidence of headache was comparable in adolescents (12 to 17 year olds) for sertraline (25.9%) versus placebo (25.5%).

Hyperkinesia has been noted in paediatric patients treated with sertraline for OCD, with an incidence of 18.4% versus 7.5% for sertraline versus placebo in 6 to 11 year olds, and 1.9% (sertraline) versus 1.8% (placebo) in 12 to 17 year olds.

Children and Adolescents with Major Depressive Disorder
Sertraline has been evaluated in paediatric MDD patients aged 6 – 17 years in two 10 week placebo controlled studies (n=364). Evidence of efficacy was not adequately demonstrated.

The following adverse events were observed in clinical trials in children and adolescents (aged 6 – 17 years old) with major depressive disorder and occurred at a frequency of at least 2% and at least twice that of placebo:

Anorexia (5.3% vs 1.1%), Dry mouth (2.1% vs 0.5%), Hyperkinesia (2.6% vs 0.5%), Tremor (2.1% vs 0%), Urinary Incontinence (2.1% vs 0%), Diarrhoea (9.5% vs 1.6%), Vomiting (4.2% vs 1.1%) and Agitation (6.3% vs 1.1%). In the trials there were a total of 17 discontinuations due to adverse events (9%) from sertraline and 4 (2.1%) from placebo. The most common reasons for discontinuation, due to adverse events, whether or not related to sertraline, were aggressive reaction (1.6%), agitation (1.6%) and suicidal ideation (1.6%), hyperkinesia (1.1%), suicide attempt (1.1%) and aggravated depression (1.1%).

The incidence of insomnia in children (6-11 years old) was 17.4% with sertraline versus 6.8% with placebo. The incidence of insomnia was comparable in adolescents (12 – 17 years old) for sertraline (10.7%) versus placebo (13.5%).

The incidence of nausea in children (6-11 years old) is 3.5% with sertraline versus 6.8 % with placebo and the incidence in adolescents (12-17 years old) is 24.3% with sertraline versus 12.5% with placebo.

In the safety analysis, events of suicide attempt were reported in the same number of patients in sertraline (2/189, 1.1%) and placebo (2/184, 1.1%) with an incidence of suicide attempts in sertraline-treated subjects of 1.1% (2 attempts in 2/189 subjects) versus 1.6% in placebo-treated subjects (3 attempts in 2/184 subjects). Suicidal ideation was reported by 3 sertraline treated patients (1.6%) and no placebo treated patients. Owing to the inherent risk of suicide attempt in patients with MDD, it is recommended to be attentive to the occurrence of suicidal thoughts.

Post-Marketing Data
Spontaneous reports of adverse events in patients receiving sertraline since market introduction have been received. They include the following:

Blood and Lymphatic System Disorders: Leucopenia and thrombocytopenia.

Immune System Disorders: Allergic reaction, allergy and anaphylactoid reaction.

Endocrine Disorders: Hyperprolactinaemia, hypothyroidism and syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and Nutrition Disorders: Appetite increased and hyponatraemia. Rare cases of hyponatraemia have been reported and appeared to be reversible when sertraline was discontinued. Some cases were possibly due to SIADH. The majority of reports were associated with older patients and patients taking diuretics or other medications.

Psychiatric Disorders: Aggressive reaction, agitation, anxiety, depersonalisation, depressive symptoms, euphoria, hallucination, libido decreased-female, libido decreased-male, nervousness, paranoia psychosis.

Nervous System Disorders: Coma, confusional state, convulsions, headache, hypoesthesia, migraine, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, teeth grinding or gait abnormalities), muscle contractions involuntary, paraesthesia and syncope. Also reported were signs and symptoms associated with serotonin syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia.

Eye Disorders: Mydriasis and vision abnormal.

Ear and Labyrinth Disorders: Tinnitus.

Cardiac Disorders: Arrhythmias (supraventricular and ventricular), palpitations and tachycardia.

Vascular Disorders: Abnormal bleeding (such as epistaxis, gastrointestinal bleeding or haematuria), hot flushes, hypertension, hypotension and orthostatic hypotension.

Respiratory, Thoracic and Mediastinal Disorders: Bronchospasm and yawning.

Gastrointestinal Disorders: Abdominal pain, constipation, pancreatitis and vomiting.

Hepato-biliary Disorders: Serious liver events (including hepatitis, jaundice and liver failure). Asymptomatic elevations in serum transaminases (ALT and AST) have been reported infrequently (0.8%) in association with sertraline administration. The abnormalities usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Skin and Subcutaneous Tissue Disorders: Alopecia, angioedema, face oedema, periorbital oedema, photosensitivity skin reaction, pruritus, purpura, rash (including rare reports of erythema multiforme and serious exfoliative skin disorders: e.g. Stevens-Johnson syndrome and epidermal necrolysis) and urticaria.

Musculoskeletal and Connective Tissue Disorders: Arthralgia and muscle cramps.

Renal and Urinary Disorders: Urinary incontinence and urinary retention.

Reproductive System and Breast Disorders: Galactorrhoea, gynecomastia, menstrual irregularities and priapism.

General Disorders and Administration Site Conditions: Asthenia, chest pain, fatigue, fever, malaise and oedema peripheral.

Investigations: Abnormal clinical laboratory results, altered platelet function, increased serum cholesterol, weight decrease and weight increase.

Other: Withdrawal reactions have been reported following the discontinuation of sertraline and common symptoms include agitation, anxiety, dizziness, headache, nausea and paraesthesia. Abrupt discontinuation of treatment with sertraline should be avoided. The majority of symptoms experienced on withdrawal of sertraline are non-serious and self-limiting.

4.9 Overdose

On the evidence available, sertraline has a wide margin of safety in overdose. Overdoses of sertraline alone of up to 8g have been reported.
Deaths involving overdoses of sertraline in combination with other drugs and/or alcohol have been reported. Therefore, any overdosage should be treated aggressively.

No specific therapy is recommended and there are no specific antidotes to sertraline. Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs 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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Sertraline is a potent and specific inhibitor of neuronal 5-HT uptake *in vitro*, but is without affinity for muscarinic, serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors.

Sertraline is devoid of stimulant, sedative, anticholinergic effect or cardiotoxicity in animals.

Unlike tricyclic antidepressants, no weight gain is observed with treatment.

5.2 Pharmacokinetic properties

Sertraline exhibits dose proportional pharmacokinetics over a range of 50-200mg. After oral administration of sertraline in man, peak blood levels occur at about 4.5-8.4 hours. Daily doses of sertraline achieve steady-state after one week. The mean half-life of sertraline for young and elderly men and women ranges from 22-36 hours. Sertraline is approximately 98% bound to plasma proteins.

The principal metabolite, N-desmethylsertraline, is inactive in *in vivo* models of depression and has a half-life of approximately 62-104 hours. Sertraline and N-desmethylsertraline are both extensively metabolised 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.

The pharmacokinetics of sertraline in elderly patients are similar to younger adults.

The pharmacokinetics of sertraline in paediatric OCD patients have been shown to be comparable with adults (although paediatric patients metabolise sertraline with slightly greater efficiency). However, lower doses may be advisable for paediatric patients given their lower body weights (especially 6-12 years), in order to avoid excessive plasma levels.

Food does not significantly change the bioavailability of Sertraline tablets.

5.3 Preclinical safety data

Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Hydroxypropylcellulose
Sodium starch glycollate (type A)
Magnesium stearate
Hypromellose
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

None.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

6.5 Nature and contents of container

Aluminium/PVC blister.

Pack sizes: 20, 28, 30, 50, (50 X 1), 98, 100.

Polyethylene container and tamper evident closure.
Pack size: 250 (dose dispensing).

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

Rowex Ltd.
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 711/84/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2006

10 DATE OF REVISION OF THE TEXT

December 2006