

Public Assessment Report
Mutual Recognition Procedure

SERTRALINE 50MG TABLETS
SERTRALINE 100MG TABLETS

UK/H/0895/001-2/MR
UK Licence No: PL 04569/0846-7

Generics (UK) Limited

LAY SUMMARY

The MHRA originally granted Focus Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Sertraline 50mg and 100mg Tablets (PL 20046/0010-11) on 1st December 2005. These applications subsequently underwent a mutual recognition procedure in Poland, which was completed on 4th September 2006. These are prescription only medicines (POM) that are used for the treatment of the following conditions:

- The symptoms of depression (feelings of sadness, tearfulness, inability to sleep or enjoy life as you once used to) and any anxiety you may have at the same time.
- Obsessive-compulsive disorder (OCD). OCD is an illness linked to anxiety in which you can become constantly troubled by persistent ideas (obsessions) that make you carry out repetitive rituals (compulsions).
- Post traumatic stress disorder (PTSD). PTSD can occur after a very emotionally traumatic experience. Some of the symptoms of PTSD are similar to depression and anxiety.

The active ingredient, sertraline, is one of a group of antidepressant or anti-obsessional medicines known as selective serotonin reuptake inhibitors (SSRIs). Low levels of a substance called serotonin in the brain are thought to be a cause of depression and these related disorders. SSRIs work by bringing the level of serotonin back up to normal.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Sertraline 50mg and 100mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

These applications have since undergone a Change of Ownership (granted on 30th October 2007) and the current marketing authorisation holder is Generics (UK) Limited (PL 04569/0846-7).

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Module 1

Product Name	Sertraline 50mg and 100mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Sertraline hydrochloride
Form	Tablets
Strength	50mg and 100mg
MA Holder	Generics UK Ltd, Station Close, Potters Bar, Hertfordshire, EN6 1TL UK.
Reference Member State (RMS)	UK
CMS	Poland
Procedure Number	UK/H/0895/001-2/MR
Timetable	Day 90 – 4 th September 2006

Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Sertraline 50 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off-white capsule shaped, film-coated tablets with 'ST/50' on one side and 'G' on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Sertraline is indicated for the treatment of symptoms of depressive illness, 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 paediatric patients with OCD.

Clinical trials in PTSD demonstrated efficacy in female patients but no evidence of efficacy was seen in males. Treatment with sertraline cannot normally therefore be recommended for male patients with PTSD. A therapeutic trial in males might on occasion be justified, but treatment should subsequently be withdrawn unless there is clear evidence of therapeutic benefit.

4.2. Posology and Method of Administration

Sertraline should be given as a single daily dose. Sertraline tablets can be administered with or without food.

Use in Adults:

Depression (including accompanying symptoms of anxiety): The starting dose is 50 mg daily and the usual antidepressant dose is 50 mg daily. In some patients, doses higher than 50 mg may be required.

Obsessive Compulsive Disorder: The starting dose is 50 mg daily, and the therapeutic dose range is 50-200 mg daily.

Post-Traumatic Stress Disorder: Treatment for PTSD should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. PTSD is a heterogeneous illness and some patient groups fulfilling the criteria for PTSD do not appear to be responsive to treatment with sertraline. Dosing should be reviewed periodically by the prescribing physician to determine response to therapy and treatment should be withdrawn if there is no clear evidence of efficacy.

Depression (including accompanying symptoms of anxiety), OCD and PTSD: In some patients doses higher than 50 mg daily may be required. In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50 mg increments over a period of weeks to a maximum of 200 mg daily.

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. The

onset of therapeutic effect may be seen within 7 days, although 2-4 weeks (and even longer in OCD) are usually necessary for full activity. A longer treatment period, even beyond 12 weeks in some cases, may be required in the case of a therapeutic trial in PTSD.

Use in children and adolescents aged 6-18 years:

Treatment should only be initiated by specialists. The safety and efficacy of sertraline has been established in paediatric OCD patients (aged 6-17). 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. Subsequent doses may be increased in case of lack of response in 50 mg/day increments up to 200 mg/day as needed. However, the generally lower body weights of children compared to adults should be taken into consideration in advancing the dose from 50 mg, in order to avoid excessive dosing. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week.

The efficacy and safety of sertraline in children and adolescents under the age of 18 years with Major Depressive Disorder have not been established. Controlled clinical studies failed to demonstrate efficacy and do not support the use of sertraline in the treatment of children and adolescents with Major Depressive Disorder.

Use in Children aged less than six years:

Sertraline is not recommended in children under six years of age since safety and efficacy have not been established. See also 'Pharmacological Properties'.

Use in the elderly:

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

4.3. Contraindications

Sertraline is contraindicated in patients with a known hypersensitivity to sertraline or to any of the excipients.

Monoamine oxidase inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA) moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of a drug interaction with 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.

Sertraline should not be used in combination with a MAOI. Sertraline may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 14 days should elapse after discontinuing sertraline treatment before starting a MAOI or RIMA.

Use in hepatic impairment: There is insufficient clinical experience in patients with significant hepatic dysfunction and accordingly sertraline should not be used in such patients.

Concomitant use in patients taking pimozide is contraindicated (see section 4.5 – Interaction with other medicaments and other forms of interaction).

4.4 Special Warnings and Special Precautions for Use

Monoamine oxidase inhibitors: See 'Contraindications'.

Use in patients with renal or hepatic impairment: As with many other medications, sertraline should be used with caution in patients with renal and hepatic impairment (see 'Contraindications').

Since sertraline is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 20-50 mL/min) or severe renal impairment (creatinine clearance <20 mL/min), single dose pharmacokinetic parameters

were not significantly different compared with controls. However, steady state pharmacokinetics of sertraline have not been adequately studied in this patient population and caution is advised when treating patients with renal 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 C_{max} in comparison with normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.

Diabetes: In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may be needed to be adjusted.

Seizures: Seizures are a potential risk with antidepressant or antiobsessional drugs. The drug should be discontinued in any patient who develops seizures. Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued if there is an increase in seizure frequency.

Electroconvulsive therapy (ECT): Since there is little clinical experience of concurrent administration of sertraline and ECT, caution is advisable.

Mania: sertraline should be used with caution in patients with a history of mania/hypomania. sertraline should be discontinued in any patient entering a manic phase.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs.

Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders.

Use in the elderly: Several hundred elderly patients have participated in clinical studies with sertraline. The pattern and incidence of adverse reactions in the elderly is similar to that in younger patients.

Use in children and adolescents under 18 years of age: Sertraline Tablets should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with obsessive-compulsive disorder. 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.

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). The 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 precaution 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 suicidal 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.

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.

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 “Undesirable effects”). 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 during 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 “Withdrawal symptoms seen on discontinuation of sertraline treatment”, Section 4.2 “Posology and method of administration”).

4.5. Interactions with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors: See 'Contraindications'.

Centrally active medication: Caution is advised if sertraline is administered with other centrally active medication. In particular, SSRIs have the potential to interact with tricyclic antidepressants leading to an increase in plasma levels of the tricyclic antidepressant. A possible mechanism for this interaction is the inhibitory effect of SSRIs on the CYP2D6 isoenzyme. There is variability among the SSRIs in the extent to which they inhibit the activity of CYP2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered drug. In formal interaction studies, chronic dosing with sertraline 50 mg daily showed minimal elevation (mean 23-37%) of steady state plasma desipramine levels (a marker of CYP2D6 isoenzyme activity).

Pimozide: Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) with sertraline coadministration. These increased levels were not associated with any changes in 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.

Alcohol: In 11 healthy subjects administered sertraline (200 mg daily) for 9 days, there was no adverse effect on cognitive or psychomotor performance relative to placebo, following a single dose of 500 mg/kg alcohol. However, the concomitant use of sertraline and alcohol in depressed patients is not recommended.

Lithium and Tryptophan: In placebo-controlled trials in normal volunteers, the co-administration of sertraline and lithium did not significantly alter lithium pharmacokinetics.

Co-administration of sertraline with lithium did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. There have been other reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of SSRIs with these drugs should be undertaken with caution.

Serotonergic drugs: There is limited controlled experience regarding the optimal timing of switching from other antidepressant or antiobsessional drugs to sertraline. Care and prudent medical judgement should be exercised when switching, particularly from long-acting agents. The duration of washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Until further data are available, serotonergic drugs, such as tramadol, sumatriptan or fenfluramine, should not be used concomitantly with sertraline, due to a possible enhancement of 5-HT associated effects.

St John's Wort: Concomitant use of the herbal remedy St John's wort (*Hypericum perforatum*) in patients receiving SSRIs should be avoided since there is a possibility of serotonergic potentiation.

Drugs that affect platelet function, such as NSAIDs: See 'Special warnings and special precautions for use (Haemorrhage)'.

Other drug interactions: Since sertraline is bound to plasma proteins, the potential of sertraline to interact with other plasma protein bound drugs should be borne in mind. Formal drug interaction studies have been performed with sertraline. Co-administration of sertraline (200 mg daily) with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters. Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction with sertraline (200 mg daily) was observed with glibenclamide or digoxin.

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

Sertraline (200 mg daily), did not potentiate the effects of carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects.

4.6. Pregnancy and lactation

Pregnancy: Although animal studies did not provide any evidence of teratogenicity, the safety of sertraline during human pregnancy has not been established. As with all drugs sertraline should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Lactation: Sertraline is known to be excreted in breast milk. Its effects on the nursing infant have not yet been established. If treatment with sertraline is considered necessary, discontinuation of breast feeding should be considered.

4.7. Effects on ability to drive and use machines

Sertraline tablets have no or negligible influence on the ability to drive and use machines.

Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However, since antidepressant or antiobsessional drugs may impair the abilities required 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 tranquillizers in patients who drive or operate machinery.

4.8. Undesirable Effects

Adverse reactions frequently occur within the first weeks of treatment and are resolved spontaneously or following dosage reduction.

The following adverse reactions are classified in terms of body systems and incidence. An incidence is defined as follows: Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10000$, $< 1/1000$), very rare ($< 1/10000$).

Classification of body systems according to MedDRA	Incidence	Adverse effects
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
Immune system disorders	Rare	Allergic reactions, hypersensitivity, anaphylactic reactions
Endocrine disorders	Rare	Hyperprolactinemia, hypothyroidism, the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Common	Anorexia
	Uncommon	Appetite increased
	Rare	Hyponatremia
Psychiatric disorders	Very common	Insomnia
	Common	Agitation, anxiety
	Uncommon	Depressive symptoms, euphoria, hallucinations
Nervous system disorders	Rare	Aggression, decreased libido in men and women, nightmares, psychotic disorders
	Very common	Dizziness, somnolence
	Common	Headache, hypesthesia, motor disturbances (including hyperkinesia, hypertonia, teeth grinding, abnormal gait), paresthesia, tremor
	Uncommon	Migraine, syncope
	Rare	Coma, seizures, voluntary muscle cramps. There have also been reports on symptoms of serotonin syndrome (in some cases they were associated with concomitant administration of serotonergic drugs) such as agitation, confusion, sweating, diarrhoea, hyperthermia, hypertension, muscular rigidity, tachycardia and psychomotor restlessness/akathisia (see section 4.4 "Special warnings and precautions for use")
	Common	Abnormal vision
Eye disorders	Uncommon	Mydriasis
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
Vascular disorders	Common	Hot flushes
	Uncommon	Arterial hypertension
	Rare	Abnormal bleeding (epistaxis, gastrointestinal bleeding, hematuria)
	Common	Yawning
Respiratory, chest and mediastinum disorders		

Classification of body systems according to MedDRA	Incidence	Adverse effects
	Rare	Bronchospasm
Gastrointestinal disorders	Very common	Diarrhoea/loose stools, dry mouth, nausea
	Common	Abdominal pain, constipation, dyspepsia, vomiting
	Rare	Pancreatitis
Hepato-biliary disorders	Rare	Severe hepatic disorders, including hepatitis, jaundice and hepatic failure; elevation in serum transaminases (AST and ALT)
Skin and subcutaneous tissue disorders	Common	Sweating increased, rash
	Uncommon	Hair loss, periorbital edema, pruritus, purpura
	Rare	Angioedema, facial edema, photosensitivity reactions, severe skin disorders (such as Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria
Musculo-skeletal and connective tissue disorders	Uncommon	Arthralgia, muscle cramps
Renal and urinary disorders	Uncommon	Urinary incontinence
	Rare	Urinary retention
Reproductive and breast disorders	Common	Sexual disturbances (mainly delayed ejaculation)
	Rare	Galactorrhea, gynecomastia, priapism
Body as a whole and local site disorders	Common	Asthenia, chest pain, fatigue
	Uncommon	Peripheral edema, increased body temperature, malaise
Investigations	Uncommon	Weight gain and weight loss
	Rare	Abnormal results of laboratory tests, altered platelet function, increased cholesterol level
Other	Rare	Symptoms associated with drug withdrawal such as agitation, anxiety, dizziness, headache, nausea have been reported
		Myasthenia, hypotension, syncope, exacerbation of Parkinson disease, xerophthalmia, diplopia, photophobia, abnormal accommodation, conjunctivitis, optic neuritis, cataract

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

Although withdrawal symptoms may occur following discontinuation of therapy, the data available from preclinical and clinical studies have not indicated the potential for abuse of selective serotonin reuptake inhibitors (SSRIs).

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 reactions. 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 section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use").

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.

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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Nervous system - Psychoanaleptics

ATC code: N06, AB06

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

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

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

Sertraline has not been observed to produce physical or psychological dependence.

Sertraline has been evaluated in paediatric OCD patients aged 6 to 17 in a 12 week placebo-controlled study. Therapy for paediatric OCD patients (aged 6-12) commenced at 25 mg/day increasing to 50 mg/day after 1 week. Side-effects which occurred significantly more frequently with sertraline than placebo were: headache, insomnia, agitation [6-12 years]; insomnia, anorexia, tremor [13-17 years]. There is limited evidence of efficacy and safety beyond 12 weeks of treatment.

5.2 Pharmacokinetic Properties

Sertraline exhibits dose proportional pharmacokinetics over a range of 50-200 mg. 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. Sertraline has a plasma half-life of approximately 26 hours with a mean half-life for young and elderly adults ranging 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 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.

A clear relationship between sertraline concentration and the magnitude of therapeutic response has not been established.

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

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**Tablet core:

Calcium hydrogen phosphate
Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate

Film coating (Opadry White Y-22-7719):

Hypromellose E464
Titanium dioxide E171
Polydextrose E1200
Triacetin
Polyethylene Glycol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store in the original package.

6.5. Nature and contents of container

High density polypropylene containers and polyethylene caps (with optional polyethylene ullage filler) in *pack sizes of 14, 15, 20, 28, 30, 50, 60, 98, 100, 250, 300, 500

PVC/PVdC/Aluminium blisters in *pack sizes of 14, 15, 20, 28, 30, 50, 60, 98, 100, 250, 300, 500

PVC/Aluminium blisters in *pack sizes of 14, 15, 20, 28, 30, 50, 60, 98, 100, 250, 300, 500

*Not all pack sizes may be marketed

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER**8. MARKETING AUTHORISATION NUMBER**

PL 04569/0846

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**10. DATE OF REVISION OF THE TEXT**

1. NAME OF THE MEDICINAL PRODUCT

Sertraline 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off-white capsule shaped, film-coated tablets with 'ST/100' on one side and 'G' on the other.

4. CLINICAL PARTICULARS**4.1. Therapeutic Indications**

Sertraline is indicated for the treatment of symptoms of depressive illness, 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 paediatric patients with OCD.

Clinical trials in PTSD demonstrated efficacy in female patients but no evidence of efficacy was seen in males. Treatment with sertraline cannot normally therefore be recommended for male patients with PTSD. A therapeutic trial in males might on occasion be justified, but treatment should subsequently be withdrawn unless there is clear evidence of therapeutic benefit.

4.2. Posology and Method of Administration

Sertraline should be given as a single daily dose. Sertraline tablets can be administered with or without food.

Use in Adults:

Depression (including accompanying symptoms of anxiety): The starting dose is 50 mg daily and the usual antidepressant dose is 50 mg daily. In some patients, doses higher than 50 mg may be required.

Obsessive Compulsive Disorder: The starting dose is 50 mg daily, and the therapeutic dose range is 50-200 mg daily.

Post-Traumatic Stress Disorder: Treatment for PTSD should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. PTSD is a heterogeneous illness and some patient groups fulfilling the criteria for PTSD do not appear to be responsive to treatment with sertraline. Dosing should be reviewed periodically by the prescribing physician to determine response to therapy and treatment should be withdrawn if there is no clear evidence of efficacy.

Depression (including accompanying symptoms of anxiety), OCD and PTSD: In some patients doses higher than 50 mg daily may be required. In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50 mg increments over a period of weeks to a maximum of 200 mg daily.

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. The onset of therapeutic effect may be seen within 7 days, although 2-4 weeks (and even longer in OCD) are usually necessary for full activity. A longer treatment period, even beyond 12 weeks in some cases, may be required in the case of a therapeutic trial in PTSD.

Use in children and adolescents aged 6-18 years:

Treatment should only be initiated by specialists. The safety and efficacy of sertraline has been established in paediatric OCD patients (aged 6-17). 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. Subsequent doses may be increased in case of lack of response in 50 mg/day increments up to 200 mg/day as needed. However, the generally lower body weights of children compared to adults should be taken into consideration in advancing the dose from 50 mg, in order to avoid excessive dosing. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week.

The efficacy and safety of sertraline in children and adolescents under the age of 18 years with Major Depressive Disorder have not been established. Controlled clinical studies failed to demonstrate efficacy and do not support the use of sertraline in the treatment of children and adolescents with Major Depressive Disorder.

Use in Children aged less than six years:

Sertraline is not recommended in children under six years of age since safety and efficacy have not been established. See also 'Pharmacological Properties'.

Use in the elderly:

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

Withdrawal symptoms seen on discontinuation of sertraline treatment:

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 "Special warnings and precautions for use" and section 4.8 "Undesirable effects"). 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

Sertraline is contraindicated in patients with a known hypersensitivity to sertraline or to any of the excipients.

Monoamine oxidase inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA) moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of a drug interaction with 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.

Sertraline should not be used in combination with a MAOI. Sertraline may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 14 days should elapse after discontinuing sertraline treatment before starting a MAOI or RIMA.

Use in hepatic impairment: There is insufficient clinical experience in patients with significant hepatic dysfunction and accordingly sertraline should not be used in such patients.

Concomitant use in patients taking pimozide is contraindicated (see section 4.5 – Interaction with other medicaments and other forms of interaction).

4.4 Special Warnings and Special Precautions for Use

Monoamine oxidase inhibitors: See 'Contraindications'.

Use in patients with renal or hepatic impairment: As with many other medications, sertraline should be used with caution in patients with renal and hepatic impairment (see 'Contraindications').

Since sertraline is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 20-50 mL/min) or severe renal impairment (creatinine clearance <20 mL/min), single dose pharmacokinetic parameters were not significantly different compared with controls. However, steady state pharmacokinetics of sertraline have not been adequately studied in this patient population and caution is advised when treating patients with renal 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 C_{max} in comparison with normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.

Diabetes: In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may be needed to be adjusted.

Seizures: Seizures are a potential risk with antidepressant or antiobsessional drugs. The drug should be discontinued in any patient who develops seizures. Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued if there is an increase in seizure frequency.

Electroconvulsive therapy (ECT): Since there is little clinical experience of concurrent administration of sertraline and ECT, caution is advisable.

Mania: sertraline should be used with caution in patients with a history of mania/hypomania. sertraline should be discontinued in any patient entering a manic phase.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs.

Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders.

Use in the elderly: Several hundred elderly patients have participated in clinical studies with sertraline. The pattern and incidence of adverse reactions in the elderly is similar to that in younger patients.

Use in children and adolescents under 18 years of age: Sertraline Tablets should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with obsessive-compulsive disorder. 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.

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). The 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 precaution 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 suicidal 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.

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.

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 "Undesirable effects"). 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 during 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 "Withdrawal symptoms seen on discontinuation of sertraline treatment", Section 4.2 "Posology and method of administration").

4.5. Interactions with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors: See 'Contraindications'.

Centrally active medication: Caution is advised if sertraline is administered with other centrally active medication. In particular, SSRIs have the potential to interact with tricyclic antidepressants leading to an increase in plasma levels of the tricyclic antidepressant. A possible mechanism for this interaction is the inhibitory effect of SSRIs on the CYP2D6 isoenzyme. There is variability among the SSRIs in the extent to which they inhibit the activity of CYP2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered drug. In formal interaction studies, chronic dosing with sertraline 50 mg daily showed minimal elevation (mean 23-37%) of steady state plasma desipramine levels (a marker of CYP2D6 isoenzyme activity).

Pimozide: Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) with sertraline coadministration. These increased levels were not associated with any changes in 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.

Alcohol: In 11 healthy subjects administered sertraline (200 mg daily) for 9 days, there was no adverse effect on cognitive or psychomotor performance relative to placebo, following a single dose of 500 mg/kg alcohol. However, the concomitant use of sertraline and alcohol in depressed patients is not recommended.

Lithium and Tryptophan: In placebo-controlled trials in normal volunteers, the co-administration of sertraline and lithium did not significantly alter lithium pharmacokinetics.

Co-administration of sertraline with lithium did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. There have been other reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of SSRIs with these drugs should be undertaken with caution.

Serotonergic drugs: There is limited controlled experience regarding the optimal timing of switching from other antidepressant or antiobsessional drugs to sertraline. Care and prudent medical judgement should be exercised when switching, particularly from long-acting agents. The duration of washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Until further data are available, serotonergic drugs, such as tramadol, sumatriptan or fenfluramine, should not be used concomitantly with sertraline, due to a possible enhancement of 5-HT associated effects.

St John's Wort: Concomitant use of the herbal remedy St John's wort (*Hypericum perforatum*) in patients receiving SSRIs should be avoided since there is a possibility of serotonergic potentiation.

Drugs that affect platelet function, such as NSAIDs: See 'Special warnings and special precautions for use (Haemorrhage)'.

Other drug interactions: Since sertraline is bound to plasma proteins, the potential of sertraline to interact with other plasma protein bound drugs should be borne in mind. Formal drug interaction studies have been performed with sertraline. Co-administration of sertraline (200 mg daily) with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters. Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction with sertraline (200 mg daily) was observed with glibenclamide or digoxin.

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

Sertraline (200 mg daily), did not potentiate the effects of carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects.

4.6. Pregnancy and lactation

Pregnancy: Although animal studies did not provide any evidence of teratogenicity, the safety of sertraline during human pregnancy has not been established. As with all drugs sertraline should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Lactation: Sertraline is known to be excreted in breast milk. Its effects on the nursing infant have not yet been established. If treatment with sertraline is considered necessary, discontinuation of breast feeding should be considered.

4.7. Effects on ability to drive and use machines

Sertraline tablets have no or negligible influence on the ability to drive and use machines.

Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However, since antidepressant or antiobsessional drugs may impair the abilities required 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 tranquillizers in patients who drive or operate machinery.

4.8. Undesirable Effects

Adverse reactions frequently occur within the first weeks of treatment and are resolved spontaneously or following dosage reduction.

The following adverse reactions are classified in terms of body systems and incidence. An incidence is defined as follows: Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10000$, $< 1/1000$), very rare ($< 1/10000$).

Classification of body systems according to MedDRA	Incidence	Adverse effects
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
Immune system disorders	Rare	Allergic reactions, hypersensitivity, anaphylactic reactions
Endocrine disorders	Rare	Hyperprolactinemia, hypothyroidism, the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Common	Anorexia
	Uncommon	Appetite increased
	Rare	Hyponatremia
Psychiatric disorders	Very common	Insomnia
	Common	Agitation, anxiety
	Uncommon	Depressive symptoms, euphoria, hallucinations
	Rare	Aggression, decreased libido in men and women, nightmares, psychotic disorders
	Very common	Dizziness, somnolence
	Common	Headache, hypesthesia, motor disturbances (including hyperkinesia, hypertonia, teeth grinding, abnormal gait), paresthesia, tremor
	Uncommon	Migraine, syncope
	Rare	Coma, seizures, voluntary muscle cramps. There have also been reports on symptoms of serotonin syndrome (in some cases they were associated with concomitant administration of serotonergic drugs) such as agitation, confusion, sweating, diarrhoea, hyperthermia, hypertension, muscular rigidity, tachycardia and psychomotor restlessness/akathisia (see section 4.4 "Special warnings and precautions for use")
	Common	Abnormal vision
Eye disorders	Uncommon	Mydriasis
	Common	Tinnitus
Ear and labyrinth disorders	Common	Tinnitus
	Common	Palpitations
Cardiac disorders	Uncommon	Tachycardia
	Common	Hot flushes
Vascular disorders	Common	Hot flushes
	Uncommon	Arterial hypertension
	Rare	Abnormal bleeding (epistaxis, gastrointestinal bleeding, hematuria)
	Common	Yawning
Respiratory, chest and mediastinum disorders	Common	Yawning

Classification of body systems according to MedDRA	Incidence	Adverse effects
	Rare	Bronchospasm
Gastrointestinal disorders	Very common	Diarrhoea/loose stools, dry mouth, nausea
	Common	Abdominal pain, constipation, dyspepsia, vomiting
	Rare	Pancreatitis
Hepato-biliary disorders	Rare	Severe hepatic disorders, including hepatitis, jaundice and hepatic failure; elevation in serum transaminases (AST and ALT)
Skin and subcutaneous tissue disorders	Common	Sweating increased, rash
	Uncommon	Hair loss, periorbital edema, pruritus, purpura
	Rare	Angioedema, facial edema, photosensitivity reactions, severe skin disorders (such as Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria
Musculo-skeletal and connective tissue disorders	Uncommon	Arthralgia, muscle cramps
Renal and urinary disorders	Uncommon	Urinary incontinence
	Rare	Urinary retention
Reproductive and breast disorders	Common	Sexual disturbances (mainly delayed ejaculation)
	Rare	Galactorrhea, gynecomastia, priapism
Body as a whole and local site disorders	Common	Asthenia, chest pain, fatigue
	Uncommon	Peripheral edema, increased body temperature, malaise
Investigations	Uncommon	Weight gain and weight loss
	Rare	Abnormal results of laboratory tests, altered platelet function, increased cholesterol level
Other	Rare	Symptoms associated with drug withdrawal such as agitation, anxiety, dizziness, headache, nausea have been reported
		Myasthenia, hypotension, syncope, exacerbation of Parkinson disease, xerophthalmia, diplopia, photophobia, abnormal accommodation, conjunctivitis, optic neuritis, cataract

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

Although withdrawal symptoms may occur following discontinuation of therapy, the data available from preclinical and clinical studies have not indicated the potential for abuse of selective serotonin reuptake inhibitors (SSRIs).

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 reactions. 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 section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use").

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.

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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Nervous system - Psychoanaleptics

ATC code: N06, AB06

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

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

Unlike tricyclic antidepressants, no weight gain is observed with treatment for depression. Sertraline has not been observed to produce physical or psychological dependence.

Sertraline has been evaluated in paediatric OCD patients aged 6 to 17 in a 12 week placebo-controlled study. Therapy for paediatric OCD patients (aged 6-12) commenced at 25 mg/day increasing to 50 mg/day after 1 week. Side-effects which occurred significantly more frequently with sertraline than placebo were: headache, insomnia, agitation [6-12 years]; insomnia, anorexia, tremor [13-17 years]. There is limited evidence of efficacy and safety beyond 12 weeks of treatment.

5.2 Pharmacokinetic Properties

Sertraline exhibits dose proportional pharmacokinetics over a range of 50-200 mg. 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. Sertraline has a plasma half-life of approximately 26 hours with a mean half-life for young and elderly adults ranging 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 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.

A clear relationship between sertraline concentration and the magnitude of therapeutic response has not been established.

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

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**Tablet core:

Calcium hydrogen phosphate
Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate

Film coating (Opadry White Y-22-7719):

Hypromellose E464
Titanium dioxide E171
Polydextrose E1200
Triacetin
Polyethylene Glycol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store in the original package.

6.5. Nature and contents of container

High density polypropylene containers and polyethylene caps (with optional polyethylene ullage filler) in *pack sizes of 14, 15, 20, 28, 30, 50, 60, 98, 100, 250, 300, 500

PVC/PVdC/Aluminium blisters in *pack sizes of 14, 15, 20, 28, 30, 50, 60, 98, 100, 250, 300, 500

PVC/Aluminium blisters in *pack sizes of 14, 15, 20, 28, 30, 50, 60, 98, 100, 250, 300, 500

*Not all pack sizes may be marketed

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER**8. MARKETING AUTHORISATION NUMBER**

PL 04569/0846

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**10. DATE OF REVISION OF THE TEXT**

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sertraline 50 mg Film-coated Tablet Sertraline 100 mg Film-coated Tablet

Sertraline Hydrochloride

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Sertraline Film-coated Tablets is and what it is used for
2. Before you use Sertraline Film-coated Tablets
3. How to use Sertraline Film-coated Tablets
4. Possible side effects
5. How to store Sertraline Film-coated Tablets
6. Further information

1. WHAT SERTRALINE FILM-COATED TABLETS IS AND WHAT IT IS USED FOR

Serotonin is a substance found naturally in the human body. If the amount of serotonin is off balance, this can lead to e.g. symptoms of depression. The active substance in Sertraline Film-coated Tablets, sertraline, inhibits the reuptake of serotonin in nerves and thus corrects the imbalance. Sertraline belongs to a group of antidepressants, which are called SSRI medicines (selective serotonin reuptake inhibitors).

Sertraline can be given to treat the following conditions:-

- the symptoms of depression
- the symptoms of a condition called Obsessive Compulsive Disorder (OCD)
- Post Traumatic Stress Disorder (PTSD).

If you are unsure why you are taking this medicine, ask your doctor.

2. BEFORE YOU USE SERTRALINE FILM-COATED TABLETS

Do not take Sertraline Film-coated Tablets:

- if you are allergic (hypersensitive) to sertraline or any of the other ingredients of Sertraline Film-coated Tablets
- if you are already taking any medicines called monoamine oxidase inhibitors (MAOI) (e.g. the antidepressants moclobemide, toloxatine and brofaromine) or if you have stopped MAOI treatment in the last two weeks.
- if you are taking medicines which contain Pimozide (an antipsychotic medicine).
- if you have impaired liver function.

Take special care with Sertraline Film-coated Tablets

You must tell your doctor before taking your medicine if:

- you have kidney or heart disease.
- you are diabetic.
- you have a history of epilepsy, as your doctor may wish to monitor you more often.
- you have a history of mental illness or are having electro-convulsive therapy (ECT)
- you have mania/hypomania.
- you have a history of bleeding disorders

Use in children and adolescents under 18 years of age

Sertraline Film-coated Tablets should normally not be used for children and adolescents under 18 years except for patients with obsessive-compulsive disorder (OCD). Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Sertraline Film-coated Tablets for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Sertraline Film-coated Tablets for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Sertraline Film-coated Tablets. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Sertraline Film-coated Tablets in this age group have not yet been demonstrated.

Thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, **contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend** that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It is especially important to tell your doctor if you are using some of the following medicines:

- MAO inhibitors (e.g. moclobemide for depression or selegiline for Parkinson's disease).
- Pimozide (antipsychotic medicine).
- other antidepressants e.g. tryptophan, amitriptyline.
- medicines for the treatment of epilepsy e.g. phenytoin.
- medicines used to treat mental illness e.g. lithium, perphenazine, thioridazine.
- herbal medicines containing St John's Wort. If you already take a St John's Wort preparation, stop taking the St John's Wort and mention it to your doctor at your next visit.
- painkillers known as NSAIDs e.g. ibuprofen, celecoxib, aspirin, diclofenac.
- anticoagulants used to thin the blood e.g. warfarin.
- antiarrhythmic heart drugs e.g. propafenone, flecainide.
- sumatriptan (for the treatment of migraine)
- tramadol (a painkiller)
- fenfluramine (a medicine that reduces appetite)
- diazepam (a muscle relaxant and a medicine that is used to treat anxiety)
- tolbutamide (for the treatment of diabetes)
- cimetidine (for the treatment of ulcers and excess stomach acid)

Taking Sertraline Film-coated Tablets with food and drink

This medicine can be taken with or without food.

DO NOT drink alcohol during treatment with sertraline.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy: There is limited experience of using sertraline during pregnancy. Therefore, sertraline should not be used during pregnancy unless clearly prescribed by a doctor.

Discuss with your doctor if you are planning to get pregnant or are pregnant.

Breast-feeding: Sertraline passes into breast milk and can affect the infant. Therefore, Sertraline Film-coated Tablets should not be used while breast-feeding unless clearly prescribed by a doctor.

Driving and using machines

DO NOT drive or operate heavy machinery if you feel less alert or drowsy.

3. HOW TO TAKE SERTRALINE FILM-COATED TABLETS

Dosage

Your doctor prescribes a suitable dosage for you. The dosage prescribed by your doctor may vary from 25 mg to 200 mg per day, although 50 mg per day is the most common dosage.

Sertraline Film-coated Tablets are taken once daily either in the morning or in the evening. This medicine can be taken with or without food. The tablets should be taken by mouth only and must not be crushed or chewed. Swallow your tablets whole with a glass of water. Try to take them at the same time every day.

Note!

Improvement will not be noticed immediately, but the effect of sertraline may occur only after 2-4 weeks treatment. If you are worried at all, go back to see your doctor.

Treatment of depression is usually continued for 6 months after improvement of condition has occurred. Treatment of panic disorders, obsessive compulsive disorders and post-traumatic stress disorder is often long-term. When improvement has occurred, treatment should be continued according to doctor's instructions.

Your doctor should not make a change to your dose more than once a week.

Children (aged less than 6 years) – Sertraline is not recommended in children under 6 years of age.

Elderly – The usual adult dose is recommended.

If you take more Sertraline Film-coated Tablets than you should

IF YOU TAKE TOO MUCH OF YOUR MEDICATION TALK TO YOUR DOCTOR OR GO TO YOUR NEAREST CASUALTY DEPARTMENT IMMEDIATELY.

If you forget to take Sertraline Film-coated Tablets

Do not take a double dose to make up for a forgotten dose, but continue using the medicine by taking the next dose on its usual administration time.

If you stop taking Sertraline Film-coated Tablets

Do not suddenly stop taking your medicine as you may suffer unpleasant side effects such as dizziness or feeling sick, numbness, headache or anxiety. If necessary, your doctor will reduce the dose slowly.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines sertraline can cause side effects, although not everybody gets them. Most side effects are usually mild and tend to wear off as you take the tablets for longer.

Very common side effects (occurs in over 1 patient in 10):

Insomnia, dizziness, drowsiness, diarrhoea/loose stools, dry mouth and nausea.

Common side effects (occurs in 1-10 patients in 100):

Eating disorders, agitation, anxiety, headache, reduced sensitivity to touch, overactive muscles, tense muscles, grinding of the teeth, abnormal walking, prickling in the skin, tremors, strange vision, ringing in the ears,

palpitations, hot flushes, yawning, stomach pains, constipation, indigestion, vomiting, increased sweating, rashes, disturbances in sexual function (mainly delayed ejaculation in men), chest pain, general weakness and tiredness.

Uncommon side effects (occurs in 1-10 patients in 1000):

Increased appetite, depression, extreme happiness, hallucinations, migraine, fainting, enlarged pupils, rapid heart rate, increased blood pressure, loss of hair, swollen eyes, itching, red spots on the skin, joint pain, muscle cramps, urinary incontinence, swelling, fever, general feeling of ill health and increase or decrease in weight.

Rare side effects (occurs in 1-10 patients in 10000):

Blood disorders, allergic reactions (these can be severe), increased sensitivity, decreased thyroid activity, changes in the production of certain hormones or enzymes, low levels of sodium in the blood, aggression, decreased sexual drive in both men and women, nightmares, mental disorders, coma, seizures, muscle cramps, agitation, confusion, sweating, diarrhoea, hyperthermia, high blood pressure, stiff muscles, increased heart rate, abnormal bleeding (e.g. nose bleeds, internal bleeding, blood in the urine), breathing difficulties, inflammation of the pancreas, severe liver disorders, swelling and allergic reactions in the skin, swelling of the face, sensitivity to light, severe skin disorders, inability to pass urine, unexpected production of milk from the nipple, development of breasts in males, abnormally long and sometimes painful erections of the penis, abnormal results of laboratory tests, increased cholesterol levels, weakness in the muscles, fainting, worsening of Parkinson's disease, eye disorders, problems with vision, sensitivity to light, feeling uncomfortable.

Cases of thoughts/behaviour of harming or killing yourself have been reported during treatment with sertraline or soon after treatment has been stopped (see section 2).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Withdrawal Symptoms

When you stop taking this medication you may experience withdrawal symptoms. This is most likely if you stop taking your medicine suddenly. Withdrawal symptoms include dizziness, tingling, numbness, difficulty in sleeping, vivid dreams, agitation, headache, tremor, feeling or being sick and anxiety. You should not stop taking your medicine abruptly and should discuss stopping your medication with your doctor.

5. HOW TO STORE SERTRALINE FILM-COATED TABLETS

Keep out of the reach and sight of children.

Store in the original container

Do not use Sertraline Film-coated Tablets after the expiry date which is stated on the package (Exp.). The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Sertraline Film-coated Tablets contains

- The active substance is sertraline hydrochloride. One tablet contains 50 mg or 100 mg of sertraline.
- The other ingredients are calcium hydrogen phosphate, microcrystalline cellulose, magnesium stearate, sodium starch glycolate, hypromellose (E464), titanium dioxide (E171), polydextrose, triacetin, and polyethylene glycol.

What Sertraline Film-coated Tablets looks like and contents of the pack

Sertraline 50 mg Film-coated Tablets:

White to off-white capsule shaped, film-coated tablets with 'ST/50' on one side and 'G' on the other.

Sertraline 100 mg Film-coated Tablets:

White to off-white capsule shaped, film-coated tablets with 'ST/100' on one side and 'G' on the other.

Sertraline 50 mg and 100 mg Film-coated Tablets are available in pack sizes of 14, 15, 20, 28, 30, 50, 60, 98, 100, 250, 300 and 500 tablets*.

*Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire, EN6 1TL.

Manufacturer: Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire, EN6 1TL.

This medicinal product is authorised in the Member States of the EEA under the following names:

Poland: Sertagen 50 mg and 100 mg

This leaflet was last approved in 08/2006

Module 4 Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton and Container Label

1. NAME OF THE MEDICINAL PRODUCT

Sertraline 50 mg Film-coated Tablet
Sertraline 100 mg Film-coated Tablet

Sertraline Hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: 50 mg sertraline as sertraline hydrochloride
Each film-coated tablet contains: 100 mg sertraline as sertraline hydrochloride

3. LIST OF EXCIPIENTS

[Not applicable]

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
15 film-coated tablets
20 film-coated tablets
28 film-coated tablets in blisters of 14
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
98 film-coated tablets
100 film-coated tablets
250 film-coated tablets
300 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use only. Do not chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use as directed by a doctor.

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[Not applicable]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Generics [UK] Limited,
Station Close
Potters Bar,
Hertfordshire
EN6 1TL,
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[Not applicable]

16. INFORMATION IN BRAILLE

[To be completed nationally]

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Sertraline 50mg and 100mg Tablets could be approved. The products are prescription-only medicines for the treatment of:

- Symptoms of depressive illness
- Treatment of obsessive compulsive disorder
- Post traumatic stress disorder
- Major depressive disorder

National marketing authorisations were granted to Focus Pharmaceuticals Limited for the medicinal products Sertraline 50mg and 100mg Tablets (PL 20046/0010-11) on 1st December 2005. A first-wave outgoing mutual recognition procedure was concluded in Poland on 4th September 2006. These applications underwent a Change of Ownership, which was completed on 30th October 2007. The current marketing authorisation holder is Generics (UK) Limited (PL 04569/0846-7).

These are applications made under Article 10.1 of 2001/83 EC, as amended, for Sertraline 50mg and 100mg Tablets, claiming essential similarity to Lustral 50mg and 100mg Tablets (Pfizer Limited, UK) which were granted UK licences over 10 years ago.

The active ingredient, sertraline, is one of a group of antidepressant or anti-obsessional medicines known as selective serotonin reuptake inhibitors (SSRIs).

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Sertraline 50mg Tablets Sertraline 100mg Tablets
Name(s) of the active substance(s) (INN)	Sertraline Hydrochloride
Pharmacotherapeutic classification (ATC code)	Nervous system – psychoanaleptics (N06 AB06)
Pharmaceutical form and strength(s)	50mg and 100mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/0895/01-02/MR
Reference Member State	United Kingdom
Member States concerned	Poland
Marketing Authorisation Number(s)	PL 04569/0846-7
Name and address of the authorisation holder	Generics UK Ltd, Station Close, Potters Bar, Hertfordshire, EN6 1TL UK.

III SCIENTIFIC OVERVIEW AND DISCUSSION

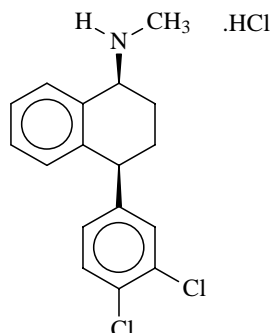
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Sertraline Hydrochloride

Chemical name: (1S-Cis)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride

Structural formula:



Molecular formula: C₁₇H₁₇Cl₂N, HCl

Appearance: A white, crystalline powder, slightly soluble in water.

Molecular weight: 342.73

Sertraline has no European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance sertraline, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

The active substance is packaged in polyethylene bags, which are placed in high density polyethylene drums and sealed.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a retest period of 2 years with the storage precautions 'Store in a well-closed container' and 'Protect from light'.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, dibasic calcium phosphate, sodium starch glycolate, water purified, magnesium stearate, Opadry II Y-22-7719 White, hydroxypropylmethylcellulose E464, titanium dioxide, polydextrose E1200 and polyethylene glycol.

All excipients comply with their European Pharmacopoeia monograph, with the exception of polyethylene glycol (which is controlled to a French National Formulary specification), and polydextrose E1200 and Opadry II Y-22-7719 White (which are controlled to suitable in-house specifications).

None of the excipients contains materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce products containing 50mg and 100mg sertraline hydrochloride that were tolerable and which could be considered as generic products to the originator products Lustral 50mg and 100mg Tablets (Pfizer Limited, UK).

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

Both strengths of tablets are packaged in (i) high-density polypropylene containers with a polyethylene cap; (ii) polyvinylchloride/polyvinylidene chloride/aluminium blisters contained in cardboard boxes; (iii) polyvinylchloride/aluminium blisters contained in cardboard boxes. Pack sizes for both strengths and all pack sizes are 14, 15, 20, 28, 30, 50, 60, 98, 100, 250, 300 and 500 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

Stability of the product

Stability studies were performed on batches of all strengths of finished product and in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies were within specified limits. These data support a shelf-life of 3 years with the storage condition 'Store in original package'.

The applicant has committed to providing stability data for the first three production-scale batches of each strength of finished product and one production-scale batch per year will be placed on stability thereafter.

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

The marketing authorisation holder has committed to updating the marketing authorisation license with a revised PIL and results of user testing, in accordance with Article 59 of Council Directive 2001/83/EC, no later than 1st July 2008.

MAA forms

The MAA forms are pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

No new preclinical data have been supplied with these applications and none are required for applications of this type.

III.3 CLINICAL ASPECTS**Clinical Pharmacology**

With the exception of the bioequivalence study comparing the proposed 100mg product to Lustral 100mg Tablets, no formal data are provided and none are required for these applications.

A randomised, single-centre, two-way, crossover study was performed comparing the proposed 100mg product versus Lustral 100mg Tablets in healthy fasted volunteers. Blood samples were taken pre- and up to 120 hours post dose, with a washout period of 14 days.

The primary parameters were C_{max} , $AUC_{0-t_{last}}$ and $AUC_{0-\infty}$; secondary were T_{max} and $T_{1/2}$.

Results from this study are presented below:

	(AUC _(0-T)) (ng.hr.ml ⁻¹)	AUC _(0-inf) (ng.hr.ml ⁻¹)	C _{max} (ng.ml ⁻¹)	C _{max} / AUC _(0-T) (hr ⁻¹ x10 ⁻²)	T _{max} (hrs)	Half-life (hrs)
Sertraline (Merck Generics)						
Arithmetic Mean (SD)	676.81 (273.50)	726.70 (287.39)	25.52 (8.44)	3.94 (0.83)	6.95 (1.33)	23.28 (6.54)
Geometric Mean	625.15	674.61	24.10	3.86	-	-
Lustral® (Pfizer Ltd, UK)						
Arithmetic Mean (SD)	661.98 (304.36)	716.45 (313.49)	25.25 (8.44)	4.09 (0.86)	6.70 (1.65)	23.02 (5.99)
Geometric Mean	601.77	657.21	23.98	3.98	-	-
Arithmetic Ratio (generic/brand)	1.02	1.01	1.01	0.96	1.04	1.01
Geometric Ratio (generic/brand)	1.04	1.03	1.01	0.97	-	-
P-value of F Ratio:						
Untransformed	-	-	-	-	-	P=0.644
Log transformed	P=0.401	P=0.526	P=0.942	P=0.400	-	-
P-Value of Shapiro-Wilk Test	P=0.3990	P=0.5955	P=0.0107	P=0.001	-	-
90% Non-parametric CI						
Two one-sided t-test (Wilcoxon-Mann-Whitney) (%)	-	-	91.18- 112.25	93.69-99.46	-	-
90% Parametric CI						
Two one-sided t-test (Schuirmann) (%)	96.21-112.18	95.72- 110.08	-	-	-	-
Power (%)*	97.8	99.1	78.8	-	-	-

- not evaluated

* calculated by Merck Generics

Note: The means presented in the table above are arithmetic (observed) means while the confidence intervals are calculated using least square means from the PROC GLM procedure of SAS®.

The 90% parametric confidence intervals of (96%-112%) for AUC_(0-T) and (96%-110%) for AUC_(0-inf), fall within the currently acceptable range of 80 to 125%. The 90% non-parametric confidence interval for C_{max} is 91%-112%, which is again within the acceptable range and satisfactory.

As the two strengths of the proposed product meet all the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence studies on the 100mg strength can be extrapolated to the 50mg strength.

Efficacy

No new data on the efficacy of sertraline hydrochloride are submitted and none are required for this type of application.

Safety

No new data on the safety of sertraline hydrochloride are submitted and none are required for this type of application.

SPC, PIL, Labels

The SPC, PIL and Labels are medically acceptable. The SPC is consistent with that for the originator products (Lustral Tablets).

Conclusion

The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Sertraline 50mg and 100mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Sertraline 100mg Tablets and the originator products Lustral 100mg Tablets (Pfizer Limited, UK). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 100mg strength can be extrapolated to the 50mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Lustral Tablets.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with sertraline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
24/10/2007	CoA	Change of Ownership from Focus Pharmaceuticals Limited (PL 20046/0010-11) to Generics (UK) Limited (PL 04569/0846-7)	Approved 30/10/2007
06/02/2008	Type II	To update Sections 2, 4.2, 4.4, 4.8 and 6.5 of the SPC following an outgoing MRP. Consequential changes to the PIL and labelling have been made	Approved 18/12/2008
05/03/2008	Type II	To update sections 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects) and 4.2 (Posology and method of administration) of the SPC and PIL with core wording as requested by Pharmacovigilance Working Party (October 2005 & June 2007).	Approved 25/07/2008
18/03/2008	Type II	Implementation of the request to include suicidal thoughts and behaviour warnings in sections 4.4 and 4.8 of the SPC following discussion at the Pharmacovigilance Working Party and CMD(h).	Approved 03/04/2008