# Public Assessment Report

# Mutual Recognition Procedure

## Sertraline 50mg Film-Coated Tablets

## Sertraline 100mg Film-Coated Tablets

## UK/H/905/01-02/MR

## UK licence no: PL 20137/0020-1

## Clarendon Pharma Limited

# LAY SUMMARY

Belgium, Czech Republic, Germany, Hungary, Italy, Malta, The Netherlands, Poland, Slovak Republic, and Slovenia approved Clarendon Pharma Limited Marketing Authorisations (licences) for the medicinal products Sertraline 50mg and 100mg Tablets. These are prescription-only medicines (POM) that are used for the treatment of major depressive episode.

This medicine contains the active substance sertraline hydrochloride which is one of the group of medicines called Selective Serotonin Re-uptake Inhibitor (SSRIs).

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.

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# Module 1

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| **Product Name** | Sertraline 50mg Tablets<br>Sertraline 100mg Tablets |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substance** | sertraline hydrochloride |
| **Form** | Film-Coated Tablets |
| **Strength** | 50mg and 100mg |
| **MA Holder** | Clarendon Pharma Limited<br>19 King Street, Seagrave, Leicestershire<br>LE12 7LY<br>United Kingdom |
| **RMS** | UK |
| **CMS** | Belgium, Czech Republic, Germany, Hungary, Italy, Malta, The Netherlands, Poland, , Slovak Republic, Slovenia |
| **Procedure Number** | UK/H/905/01-02/MR |
| **Timetable** | Day 90- 02/08/2007 |

# Module 2

# Summary of Product Characteristics

**1. NAME OF THE MEDICINAL PRODUCT**
Sertraline 50mg Film-Coated Tablets

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated tablet contains 50mg sertraline (as sertraline hydrochloride).

For excipients, see 6.1.

**3. PHARMACEUTICAL FORM**
Film-coated tablet

Oblong, biconvex, white tablet with "SR50" on one side and " | " on the other. The tablet can be divided into equal halves.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**
Treatment of major depressive episodes.

**4.2 Posology and method of administration**
Adults

Major depressive episodes.

The usual daily dose is 50 mg sertraline.

If required, the dose can be increased to 100 mg sertraline/day. The maximum daily dose is 200 mg sertraline.

If dose increments are required, these should be made in steps of 50 mg at minimum intervals of 1 week. Dose changes should not be performed more than once per week due to elimination half-life of sertraline over 24 hours.

During long term therapy the aim is to administer the lowest possible dosage which provides adequate therapeutic efficacy.

Method and duration of administration:

Sertraline should be taken once daily, mornings or evenings, with sufficient liquid. The tablets may be taken at mealtimes or independently of food intake. For doses not realisable/practicable with this strength other strengths/pharmaceutical forms are available.

The onset of antidepressant effects may occur within 7 days, however, the maximum effect is generally reached after 2 to 4 weeks of treatment; it is advisable that the patients are informed of this.

The duration of treatment depends upon the nature and severity of the disorder. After remission of the symptoms of depression long term therapy for the control of remission (at least 6 months) may be required.

Use in children and adolescents under 18 years of age:

Sertraline Film-coated Tablets should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4)

Elderly:

As the elimination half life may be prolonged in elderly patients, it should be advised that the dosage should be as low as possible in the elderly.

Patients with impaired hepatic function:

In patients with impaired hepatic function sertraline should be used with caution. Although it is not clear if dosage adjustments are necessary in case of impaired hepatic function, it is recommended that the dose is reduced or the interval between doses prolonged. Sertraline should not be used in case of severe hepatic impairment as no clinical data are available.

Patients with impaired renal function:

Impairment of renal function does not necessitate an adjustment of the dose (also see section 4.4). Patients with severe renal impairment should be closely monitored in long term therapy.

Withdrawal symptoms seen on discontinuation:

Abrupt discontinuation should be avoided. When stopping treatment with Sertraline Film-coated Tablets the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 and section 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

**4.3 Contraindications**

- Hypersensitivity to sertraline or any of the excipients
- Sertraline must not be used concurrently with monoamine oxidase inhibitors (MAOI's) including the selective MAOI selegiline and the reversible MAOI (RIMA) moclobemide (see section 4.4 and section 4.5)
- Sertraline must not be used concurrently with pimozide (see section 4.5)

**4.4 Special warnings and precautions for use**

*Use in children and adolescents under 18 years of age:*

Sertraline Film-coated Tablets should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo.

If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Serotonin syndrome: On rare occasions development of a serotonin syndrome (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) may occur in association with treatment of sertraline, particularly when given in combination with MAO inhibitors or other serotonergic medicinal products. As this syndrome may result in potentially life-threatening conditions, treatment with sertraline should be discontinued if such events occur and supportive symptomatic treatment should be initiated.

MAO inhibitors: Concomitant treatment with serotonin re-uptake inhibitors and MAO inhibitors including the irreversible MAO inhibitor selegiline and the reversible MAO inhibitor moclobemide is contraindicated because fatal reactions have been reported in patients receiving sertraline in combination with a MAO inhibitor.

Treatment with sertraline can be initiated at the earliest two weeks after discontinuation of an irreversible MAO inhibitor (e.g. selegiline), or at least 24 hours after discontinuation of a reversible MAO inhibitor with a short half-life (e.g. moclobemide). At least two weeks should elapse between discontinuation of sertraline and initiation of therapy with any MAO inhibitor. The dosage of sertraline should be increased gradually until an optimal response is reached.

Serotonergic medicinal products: Concomitant administration of sertraline with other medicinal products which potentiate the serotonergic neurotransmission, e.g. tryptophan, fenfluramin, dextromethorphan, pethidine, tramadol, serotonin-agonists, and other SSRIs should only take place with great caution and, if possible be avoided. (see section 4.5).

A changeover from use of selective serotonin reuptake inhibitors or other antidepressants should be done cautiously in order to avoid possible pharmacodynamic interactions (see section 4.5). Careful clinical monitoring is of especial importance when sertraline is initiated after discontinuation of an antidepressant with long half-life such as e.g. fluoxetine. There is no well documented evidence of the duration of treatment free interval needed during changeover from one antidepressant to another (see also section 4.5).

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

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

Patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. In addition, there is a possibility of an increased risk of suicidal behaviour in young adults.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of such events and to seek medical advice immediately if these symptoms present.

Activation of mania / hypomania:
In approximately 0.4 % of patients treated with sertraline in clinical studies mania or hypomania has been reported. Therefore sertraline should be used with caution in patients with a history of mania / hypomania. Close surveillance by the physician is required. Sertraline should be discontinued in any patient entering a manic phase.

Schizophrenia:
Psychotic symptoms might become aggravated in schizophrenic patients.

Withdrawal symptoms seen on discontinuation:
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8).

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 and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported following discontinuation of SSRIs/SNRIs. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that sertraline should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal symptoms seen on discontinuation, section 4.2).

Washout period of SSRI

When switching from one SSRI to another, the duration of the washout period should be determined with regard to the elimination half life of the previous product.

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 anticoagulants, medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders (also see section 4.5).

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

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemic control. Blood glucose levels should be checked regularly. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Cardiac disease:
The safety of sertraline has not been established in patients who have recently suffered a heart attack or patients with instable cardiac disease. Patients diagnosed with these disorders were excluded from clinical studies. The electrocardiograms of patients receiving sertraline in double-blind clinical studies indicate that sertraline is not associated with significant ECG abnormalities.

Elderly:
The pattern and incidence of undesirable effects in the elderly are comparable to the effects in younger patients. The elderly may be, however, often more sensitive to the undesirable effects of antidepressants.

Impaired hepatic function:
Sertraline is extensively metabolised in the liver. A pharmacokinetic study of repeated doses in patients with mild and stabilised cirrhosis revealed a prolonged elimination half life and an approximately three times greater AUC and maximum plasma concentration (Cmax) compared to patients with normal liver function. No significant difference in plasma protein binding was observed between the groups. Sertraline should not be used in patients with severe hepatic impairment (for sertraline in patients with hepatic impairment see section 4.2).

Impaired renal function:
As a result of the extensive hepatic metabolism only a negligible portion of sertraline is eliminated unchanged via the renal pathway. In patients with mild to moderate (creatinine clearance 30 to 60 ml/min) or moderate to severe (creatinine clearance 10 to 29 ml/min) impairment of renal function the pharmacokinetic parameters (AUC0-24 and Cmax), after repeated doses, were not found to differ significantly from those in patients with normal renal function. The half-lives were similar, and no differences in plasma protein binding could be established between the groups studied. This study shows that, as would be expected in view of the low renal elimination rate, the dosage of sertraline does not have to be adjusted in case of impaired renal function.

Convulsive disorders:
Experience in treating of epileptic patients is limited. Therefore treatment should be avoided in patients with unstable epilepsy, and patients with stable epilepsy should be carefully monitored and the treatment should be discontinued if seizures occur.

Akathisia / Psychomotor restlessness
The use of Sertraline Film-coated Tablets has been associated with the development of akathisia, characterized 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.

**4.5 Interaction with other medicinal products and other forms of interaction**
Contraindications:

MAO inhibitors:
Sertraline should not be used concomitantly with MAO inhibitors, including the irreversible MAO inhibitor selegiline and the reversible MAO inhibitor moclobemide, see sections 4.3 and 4.4.

Pimozide:
Increased pimozide levels have been observed in a clinical study after concomitant administration of sertraline and a low single dose of pimozide (2 mg). These increased levels have not been associated with ECG-changes. The mechanism of this interaction is unknown. The concomitant administration of sertraline and pimozide is contraindicated, because co-administration results in increased pimozide plasma levels, and as a consequence may increase the risk of arrhythmias and prolongation of QT-interval associated with pimozide treatment (also see section 4.3).

Concomitant administration with sertraline not recommended:

Serotonergic substances:
In view of the fact that insufficient data are available, serotonergic substances, such as tryptophan, fenfluramine, dextromethrophan, pethidine, tramadol and serotonin agonists, should not be used concurrently with Sertraline (see section 4.4).

Hypericum perforatum:
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.

Precautions:

Other medicinal products:

Active substances bound to plasma proteins
Due to high protein binding of sertraline the interactions with other substances highly bound to plasma proteins are possible. However, in three interaction studies, sertraline had no significant effects on the plasma protein binding of diazepam, tolbutamide and warfarin.

Other interactions observed in studies:
Concomitant administration of sertraline and diazepam or tolbutamide resulted in slight, but statistically significant changes to various pharmacokinetic parameters. Cimetidine reduced the rate of elimination of concurrently administered sertraline. The clinical relevance of these effects is unclear. Sertraline had no influence on the efficacy of atenolol; there were no interactions with glibenclamide or digoxin.

Lithium:
On concomitant administration of lithium and sertraline in placebo-controlled studies in healthy subjects, there were no changes in the pharmacokinetics of lithium, although there was an increased incidence of tremor in comparison with patients receiving placebo, indicating that there may be a pharmacodynamic influence. Patients receiving lithium and sertraline or other substances with a serotonergic mode of action should be appropriately monitored.

Sumatriptan:
In rare cases, weakness, hyperreflexia, lack of coordination, confusion, anxiety and agitation have been reported in association with the concomitant use of sertraline and sumatriptan. Patients in whom it is clinically necessary to administer sertraline and sumatriptan concurrently should be appropriately monitored.

CNS active substances and alcohol:
Concomitant treatment with sertraline 200 mg daily did not increase the effect of alcohol, carbamazepine, haloperidol or phenytoin on psychomotor and cognitive functions in healthy volunteers. However, consumption of alcohol in conjunction with sertraline treatment is not recommended.

Hypoglycaemic substances:
Sertraline may alter glycaemic control. Therefore it is advisable to monitor the blood glucose level when initiating sertraline for diabetic patients. See section 4.4.

Oral anticoagulants, salicylic acid derivates and NSAID:

On concomitant administration of sertraline and warfarin there was a slight, but statistically significant, increase in prothrombin time; close monitoring of prothrombin time is thus advisable when therapy with Sertraline tablets is initiated or terminated (see "active substances bound to plasma proteins" and "Cytochrome P450 interactions / 2C9). There may potentially be an increased risk of bleeding when SSRIs are combined with other oral anticoagulants, salicylic acid derivatives NSAID, atypical antipsychotics, phenothiazines, and most tricyclic antidepressants (see section 4.4).

Diuretics
Diuretics used concomitantly with sertraline may predispose (elderly patients) to hyponatraemia and SIADH.

Medicinal products metabolised by cytochrome P450-enzymes:
CYP 2D6: In interaction studies, there was only a minimal increase in steady-state plasma concentrations of desipramine (23 – 37 % on average) during long term use of sertraline at a dose of 50 mg/day. Desipramine is a marker for cytochrome P450 (CYP) 2D6 isoenzyme activity.
CYP 3A3/4: In vivo interaction studies have shown that long term administration of sertraline at a dose of 200 mg daily does not result in inhibition of CYP 3A3/4mediated 6-β-hydroxylation of endogenous cortisol or metabolism of carbamazepine and terfenadine. There was no inhibition of the CYP 3A3/4-mediated metabolism of alprazolam during long term use of 50 mg/day sertraline. The results of these studies indicate that there is no clinically relevant inhibition of CYP 3A3/4 activity by sertraline.
-CYP 2C9: The lack of any clinically significant effects of long term administration of 200 mg sertraline/day on plasma concentrations of tolbutamide, phenytoin and warfarin shows that sertraline does not inhibit CYP 2C9 to any clinically relevant extent.
CYP 2C19: The lack of any clinically significant effects of long term administration of 200 mg sertraline/day on plasma concentrations of diazepam allows the conclusion that sertraline does not inhibit CYP 2C19 to any clinically relevant extent.
CYP 1A2: In vitro investigations have demonstrated that sertraline has little or no potential for inhibition of CYP 1A2.

Phenytoin:
Although no clinically significant inhibition of the metabolism of phenytoin was observed in a placebo controlled study in healthy subjects, it is advisable to monitor plasma phenytoin concentrations on initiation of sertraline therapy and to adjust the phenytoin dose as appropriate. Concomitant administration of phenytoin can reduce plasma sertraline levels.

Changeover from use of selective serotonin re-uptake inhibitors or other antidepressants: See section 4.4

Antipyrine:
The half-life of antipyrine is reduced by concomitant administration of sertraline, which points to a clinically non-significant hepatic enzyme induction.

**4.6 Pregnancy and lactation**

Pregnancy
Data on a limited number (n = 147) of exposed pregnant women indicate no undesirable effects of sertraline on pregnancy or on the health of the foetus. Animal studies did not provide any evidence of teratogenic effects of sertraline, however embryotoxicity has been observed (see section 5.3). New born infants should be observed if maternal use of sertraline continues into the later stages of pregnancy, particularly the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the new born infants after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

Sertraline should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Women of childbearing age should use a method of contraception if they are receiving sertraline.

Lactation: Sertraline is known to be excreted in breast milk (milk/plasma-ratio approximately 1.8). Very low or non-detectable plasma concentrations of sertraline have been determined in breastfed infants. Sertraline should only be administered during lactation if the expected benefit outweighs potential risk to the child.

**4.7 Effects on ability to drive and use machines**

If used as recommended, Sertraline may in isolated cases alter reactions to such an extent, that the ability to drive and use machines, or to work in potentially hazardous situations is impaired. This applies particularly on commencement of therapy, change of medication and on concomitant ingestion of alcohol or medicinal products which influence the function of the central nervous system. The patient should be warned not to drive or work in potentially hazardous situations until the individual effects of sertraline are known.

**4.8 Undesirable effects**

| Organ System Disorder | Very common (≥1/10) | Common (≥1/100 and <1/10) | Uncommon (≥1/1000 and <1/100) | Rare (≥1/10000 and <1/1000) |
|---|---|---|---|---|
| Blood and lymphatic system disorders: | | | purpura, altered platelet function, altered haemorrhagic diathesis (with e.g. epistaxis, gastrointestinal haemorrhage or haematuria) | leukopenia, thrombocytopenia |
| Endocrine disorders: | | | | gynecomastia, hyperprolactinaemia, galactorrhoea, hypothyroidism, syndrome of inappropriate ADH secretion |
| Metabolism and nutrition disorders: | | | | hyponatraemia: this remitted on discontinuation of therapy. Isolated cases may have been attributable to syndrome of inappropriate ADH secretion. These undesirable effects have mainly occurred in elderly patients and in patients using diuretics or other medicinal products. Elevated serum cholesterol levels. |
| Psychiatric disorders: | insomnia, somnolence, anorexia: | yawning, agitation, anxiety | euphoria, depressive symptoms, hallucinations, mania, hypomania | loss of libido (in women and men), nightmares, aggressive reactions, psychosis, suicidal thoughts/behaviour (see section 4.4) |
| Nervous system disorders: | tremor, dizziness, dry mouth | headache, motor disorders (including extrapyramidal symptoms, such as hyperkinesia, increased muscle tone, teeth-grinding and impaired gait), paraesthesiae, hypaesthesia, increased sweating | migraine. | involuntary muscle contractions, coma, seizures, psychomotor restlessness/akathisia (see section 4.4), signs and symptoms associated with serotonin syndrome: agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia. In some cases, these symptoms occurred in association with the concomitant use of serotonergic agents |
| Eye disorders: | | impaired vision | mydriasis | |
| Ear and labyrinth disorders: | | tinnitus | | |
| Cardiac disorders: | | chest pain, palpitations | hypertension, syncope, tachycardia | |
| Vascular disorders: | | | peripheral oedema, peri-orbital oedema, | |

| Organ System Disorder | Very common (≥1/10) | Common (≥1/100 and <1/10) | Uncommon (≥1/1000 and <1/100) | Rare (≥1/10000 and <1/1000) |
|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | | bronchospasm |
| Gastrointestinal disorders: | nausea, diarrhoea / loose stool | dyspepsia, obstipation, abdominal pain, vomiting | increased appetite, pancreatitis | |
| Hepatobiliary disorders | | | severe hepatic disorders (including hepatitis, jaundice and liver failure), asymptomatic elevation of serum transaminases (SGOT and SGPT). Alterations to transaminase levels mainly occurred in the initial 9 weeks of treatment and rapidly disappeared after discontinuation of therapy. | |
| Skin and subcutaneous tissue disorders | | skin rash | pruritus, alopecia, erythema multiforme | photosensitivity of skin, urticaria, Quincke's oedema, severe dermal exfoliation e.g. Stevens-Johnson-syndrome and epidermal necrolysis |
| Musculoskeletal, connective tissue and bone disorders: | | | arthralgia | |
| Renal and urinary disorders: | | | urinary incontinence | facial oedema, urinary retention |
| Reproductive system and breast disorders: | sexual disorders (mainly delayed ejaculation in men) | menstrual disorders | | priapism |
| General disorders: | | asthenia, tiredness, hot flushes | indisposition, gain of body weight, loss of body weight, fever | Rare: anaphylactoid reaction, allergic reactions, allergy |
| Investigations: | | | abnormal laboratory values | |

Withdrawal symptoms seen on discontinuation: Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported. Generally these events are mild to moderate and are self-limiting. However, in some patients they may be severe and/or prolonged. It is therefore advised that when treatment with sertraline is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

More than 700 elderly patients (aged >65 years) participated in a clinical study to demonstrate the efficacy of sertraline in this patient group. The types and frequency of undesirable effects in the elderly patients were similar to those in younger patients.

**4.9 Overdose**

Symptoms of overdose
The symptoms of sertraline overdose take the form of serotonin-mediated side-effects such as drowsiness, gastrointestinal disorders (e.g. nausea and vomiting), tachycardia, tremor, agitation and dizziness. Coma has been reported in rare cases.

Toxicity
Available data show that sertraline has a broad safety index on overdose. There are reports of ingestion of up to 13.5 g sertraline alone. Fatality mainly occurred after sertraline intoxication when other medications and/or alcohol were ingested concomitantly. It is thus advisable to take an aggressive approach in the treatment of overdose.

Treatment
There is no known specific antidote to sertraline. The following measures are recommended: ensure airways are free and adequate ventilation and O2 therapy are provided. Administration of activated charcoal, in combination with sorbitol solution or another purgative if necessary, is at least as effective as gastric lavage. Induction of vomiting is not advisable. General monitoring of cardiovascular function is advisable and general supportive measures should be provided. Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be effective in view of the large volume of distribution of sertraline.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antidepressants, Selective serotonin reuptake inhibitors

ATC: N06A B06

It is postulated that depressive disorders are associated with a disturbance of 5hydroxytryptamine (serotonin) metabolism in the brain. It has been demonstrated in vitro that sertraline is a potent and selective inhibitor of neuronal reuptake of serotonin: this resulted in a potentiation of the physiological effects of the substance in animal models. Sertraline has only very weak effects on neuronal uptake of norepinephrine and dopamine. At clinically effective doses, sertraline inhibits the uptake of serotonin by human blood platelets.

In animal studies, sertraline has been shown to have no stimulating, sedative or anticholinergic / cardiotoxic effects. In experimental investigations conducted in healthy subjects, sertraline exhibited no sedative potential and did not affect psychomotor performance.

As a result of its selective inhibition of serotonin reuptake, sertraline does not influence catecholamine activity. In addition, sertraline has no affinity for muscarinergic, serotonergic, dopaminergic, histaminergic, benzodiazepine, GABA or adrenergic receptors. As in the case of other clinically effective antidepressants, there was downregulation of the responsiveness of cerebral norepinephrine receptors with long term use of sertraline.

No potential for the misuse or abuse of sertraline is reported from human and animals studies

### 5.2 Pharmacokinetic properties
Absorption:
The pharmacokinetic profile of sertraline is proportional to dose over the range 50 – 200 mg. After single oral daily administration of 50 – 200 mg sertraline for 14 days, peak plasma concentrations were reached after 4.5 – 8.4 hours. On the basis of recovery rates in urine and faeces, it can be estimated that absorption after oral administration is at least 70 %. Bioavailability is reduced by the first pass effect. Concomitant consumption of food does not significantly influence the bioavailability of sertraline tablets.

Distribution:
Plasma protein binding of sertraline is approximately 98 %. Data from animal studies indicate that sertraline has a large volume of distribution. Steady-state concentrations are thus reached after approximately 1 week and sertraline concentrations are doubled compared to plasma levels after initial dose with once daily administration.

Metabolism:

Sertraline and the main metabolite, N-desmethylsertraline both undergo extensive hepatic metabolism. In vitro N-desmethylsertraline exhibits considerably less (by a factor of approximately 20) activity than the parent substance. The metabolite had no effect in in vivo depression models.

It has been demonstrated in in vitro investigations that the metabolism of sertraline is mainly mediated by the CYP 3A4 enzyme, with only limited involvement of CYP 2D6. At the standard dose of 50 mg, sertraline has only limited effects on the CYP 2D6- and CYP 3A4mediated metabolism of other substances.

Excretion:
The mean terminal elimination half-life of sertraline is approximately 26 hours. The half-life of N-desmethylsertraline is 62 – 104 hours, so that plasma concentrations of the metabolite reach the same level as the parent substance.

The metabolites of sertraline and N-desmethylsertraline are eliminated in equal fractions in faeces and urine. Only a small percentage (less than 0.2 %) of unchanged sertraline is recovered in urine.

Elderly:
The pharmacokinetic profile of sertraline in elderly patients is similar to that in younger patients.

Hepatic insufficiency:
For pharmacokinetics of sertraline in patients with cirrhosis see sections 4.2 and 4.4.

**5.3 Preclinical safety data**

Conventional preclinical studies on sertraline did not demonstrate mutagenicity nor carcinogenicity. No teratogenic effects have been observed in studies on reproduction toxicity in rats and rabbits. However, delay of ossification occurred in foetus of rats and rabbits in dosages exceeding the maximal therapeutic dose in humans 2.5- up to 10-fold. Administration of sertraline in rats during the last third of gestation till end of lactation in a dosage exceeding the maximal therapeutic dose in humans 5-fold resulted in an increased number of stillbirths as well as in decreased survival rate and body weight of descendants. It could be demonstrated that lower survival rate of descendants is implicated by intrauterine exposure.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

In the tablet core:
Microcrystalline cellulose
Dibasic calcium phosphate dihydrate
Hydroxypropylcellulose
Sodium starch glycolate (Type A)
Magnesium stearate

In the tablet film-coat:
Opadry white YS-1R-7003
Containing:
Hypromellose
Macrogol
Titanium dioxide (E171)
Polysorbate 80

Opadry clear YS-1R-7006
Containing:
Hypromellose
Macrogol

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**
PVC/PVdC aluminium foil blisters

Pack sizes of 7, 14, 20, 28, 30, 35 49, 50, 50 x 1 (unit dose), 98, 100, 250 and 294 film-coated tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**
No special requirements.

**7. MARKETING AUTHORISATION HOLDER**
Clarendon Pharma Limited
19 King Street, Seagrave
Leicestershire
LE12 7LY
United Kingdom

**8. MARKETING AUTHORISATION NUMBER**
PL 20137/0020

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT.**

**1. NAME OF THE MEDICINAL PRODUCT**
Sertraline 100mg Film-Coated Tablets

**3. QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated tablet contains 100mg sertraline (as sertraline hydrochloride).

For excipients, see 6.1.

**3. PHARMACEUTICAL FORM**
Film-coated tablet

Oblong, biconvex, white tablet with **"**SR100**"** on one side and blank on the other.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**
Treatment of major depressive episodes.

**4.3 Posology and method of administration**
Adults

Major depressive episodes.

The usual daily dose is 50 mg sertraline.

If required, the dose can be increased to 100 mg sertraline/day. The maximum daily dose is 200 mg sertraline.

If dose increments are required, these should be made in steps of 50 mg at minimum intervals of 1 week. Dose changes should not be performed more than once per week due to elimination half-life of sertraline over 24 hours.

During long term therapy the aim is to administer the lowest possible dosage which provides adequate therapeutic efficacy.

Method and duration of administration:

Sertraline should be taken once daily, mornings or evenings, with sufficient liquid. The tablets may be taken at mealtimes or independently of food intake. For doses not realisable/practicable with this strength other strengths/pharmaceutical forms are available.

The onset of antidepressant effects may occur within 7 days, however, the maximum effect is generally reached after 2 to 4 weeks of treatment; it is advisable that the patients are informed of this.

The duration of treatment depends upon the nature and severity of the disorder. After remission of the symptoms of depression long term therapy for the control of remission (at least 6 months) may be required.

Use in children and adolescents under 18 years of age:

Sertraline Film-coated Tablets should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4)

Elderly:

As the elimination half life may be prolonged in elderly patients, it should be advised that the dosage should be as low as possible in the elderly.

Patients with impaired hepatic function:

In patients with impaired hepatic function sertraline should be used with caution. Although it is not clear if dosage adjustments are necessary in case of impaired hepatic function, it is recommended that the dose is reduced or the interval between doses prolonged. Sertraline should not be used in case of severe hepatic impairment as no clinical data are available.

Patients with impaired renal function:

Impairment of renal function does not necessitate an adjustment of the dose (also see section 4.4). Patients with severe renal impairment should be closely monitored in long term therapy.

Withdrawal symptoms seen on discontinuation:

Abrupt discontinuation should be avoided. When stopping treatment with Sertraline Film-coated Tablets the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 and section 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

**4.3 Contraindications**

- Hypersensitivity to sertraline or any of the excipients
- Sertraline must not be used concurrently with monoamine oxidase inhibitors (MAOI's) including the selective MAOI selegiline and the reversible MAOI (RIMA) moclobemide (see section 4.4 and section 4.5)
- Sertraline must not be used concurrently with pimozide (see section 4.5)

**4.4 Special warnings and precautions for use**

*Use in children and adolescents under 18 years of age:*

Sertraline Film-coated Tablets should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo.

If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Serotonin syndrome: On rare occasions development of a serotonin syndrome (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) may occur in association with treatment of sertraline, particularly when given in combination with MAO inhibitors or other serotonergic medicinal products. As this syndrome may result in potentially life-threatening conditions, treatment with sertraline should be discontinued if such events occur and supportive symptomatic treatment should be initiated.

MAO inhibitors: Concomitant treatment with serotonin re-uptake inhibitors and MAO inhibitors including the irreversible MAO inhibitor selegiline and the reversible MAO inhibitor moclobemide is contraindicated because fatal reactions have been reported in patients receiving sertraline in combination with a MAO inhibitor.

Treatment with sertraline can be initiated at the earliest two weeks after discontinuation of an irreversible MAO inhibitor (e.g. selegiline), or at least 24 hours after discontinuation of a reversible MAO inhibitor with a short half-life (e.g. moclobemide). At least two weeks should elapse between discontinuation of sertraline and initiation of therapy with any MAO inhibitor. The dosage of sertraline should be increased gradually until an optimal response is reached.

Serotonergic medicinal products: Concomitant administration of sertraline with other medicinal products which potentiate the serotonergic neurotransmission, e.g. tryptophan, fenfluramin, dextromethorphan, pethidine, tramadol, serotonin-agonists, and other SSRIs should only take place with great caution and, if possible be avoided. (see section 4.5).

A changeover from use of selective serotonin reuptake inhibitors or other antidepressants should be done cautiously in order to avoid possible pharmacodynamic interactions (see section 4.5). Careful clinical monitoring is of especial importance when sertraline is initiated after discontinuation of an antidepressant with long half-life such as e.g. fluoxetine. There is no well documented evidence of the duration of treatment free interval needed during changeover from one antidepressant to another (see also section 4.5).

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

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

Patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. In addition, there is a possibility of an increased risk of suicidal behaviour in young adults.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of such events and to seek medical advice immediately if these symptoms present.

Activation of mania / hypomania:
In approximately 0.4 % of patients treated with sertraline in clinical studies mania or hypomania has been reported. Therefore sertraline should be used with caution in patients with a history of mania / hypomania. Close surveillance by the physician is required. Sertraline should be discontinued in any patient entering a manic phase.

Schizophrenia:
Psychotic symptoms might become aggravated in schizophrenic patients.

Withdrawal symptoms seen on discontinuation:
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8).

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 and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported following discontinuation of SSRIs/SNRIs. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that sertraline should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal symptoms seen on discontinuation, section 4.2).

Washout period of SSRI

When switching from one SSRI to another, the duration of the washout period should be determined with regard to the elimination half life of the previous product.

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 anticoagulants, medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders (also see section 4.5).

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

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemic control. Blood glucose levels should be checked regularly. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Cardiac disease:
The safety of sertraline has not been established in patients who have recently suffered a heart attack or patients with instable cardiac disease. Patients diagnosed with these disorders were excluded from clinical studies. The electrocardiograms of patients receiving sertraline in double-blind clinical studies indicate that sertraline is not associated with significant ECG abnormalities.

Elderly:
The pattern and incidence of undesirable effects in the elderly are comparable to the effects in younger patients. The elderly may be, however, often more sensitive to the undesirable effects of antidepressants.

Impaired hepatic function:
Sertraline is extensively metabolised in the liver. A pharmacokinetic study of repeated doses in patients with mild and stabilised cirrhosis revealed a prolonged elimination half life and an approximately three times greater AUC and maximum plasma concentration (Cmax) compared to patients with normal liver function. No significant difference in plasma protein binding was observed between the groups. Sertraline should not be used in patients with severe hepatic impairment (for sertraline in patients with hepatic impairment see section 4.2).

Impaired renal function:
As a result of the extensive hepatic metabolism only a negligible portion of sertraline is eliminated unchanged via the renal pathway. In patients with mild to moderate (creatinine clearance 30 to 60 ml/min) or moderate to severe (creatinine clearance 10 to 29 ml/min) impairment of renal function the pharmacokinetic parameters (AUC0-24 and Cmax), after repeated doses, were not found to differ significantly from those in patients with normal renal function. The half-lives were similar, and no differences in plasma protein binding could be established between the groups studied. This study shows that, as would be expected in view of the low renal elimination rate, the dosage of sertraline does not have to be adjusted in case of impaired renal function.

Convulsive disorders:
Experience in treating of epileptic patients is limited. Therefore treatment should be avoided in patients with unstable epilepsy, and patients with stable epilepsy should be carefully monitored and the treatment should be discontinued if seizures occur.

Akathisia / Psychomotor restlessness
The use of Sertraline Film-coated Tablets has been associated with the development of akathisia, characterized 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.

**4.5 Interaction with other medicinal products and other forms of interaction**
Contraindications:

MAO inhibitors:
Sertraline should not be used concomitantly with MAO inhibitors, including the irreversible MAO inhibitor selegiline and the reversible MAO inhibitor moclobemide, see sections 4.3 and 4.4.

Pimozide:
Increased pimozide levels have been observed in a clinical study after concomitant administration of sertraline and a low single dose of pimozide (2 mg). These increased levels have not been associated

with ECG-changes. The mechanism of this interaction is unknown. The concomitant administration of sertraline and pimozide is contraindicated, because co-administration results in increased pimozide plasma levels, and as a consequence may increase the risk of arrhythmias and prolongation of QT-interval associated with pimozide treatment (also see section 4.3).

Concomitant administration with sertraline not recommended:

Serotonergic substances:
In view of the fact that insufficient data are available, serotonergic substances, such as tryptophan, fenfluramine, dextromethrophan, pethidine, tramadol and serotonin agonists, should not be used concurrently with Sertraline (see section 4.4).

Hypericum perforatum:
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.

Precautions:

Other medicinal products:

Active substances bound to plasma proteins
Due to high protein binding of sertraline the interactions with other substances highly bound to plasma proteins are possible. However, in three interaction studies, sertraline had no significant effects on the plasma protein binding of diazepam, tolbutamide and warfarin.

Other interactions observed in studies:
Concomitant administration of sertraline and diazepam or tolbutamide resulted in slight, but statistically significant changes to various pharmacokinetic parameters. Cimetidine reduced the rate of elimination of concurrently administered sertraline. The clinical relevance of these effects is unclear. Sertraline had no influence on the efficacy of atenolol; there were no interactions with glibenclamide or digoxin.

Lithium:
On concomitant administration of lithium and sertraline in placebo-controlled studies in healthy subjects, there were no changes in the pharmacokinetics of lithium, although there was an increased incidence of tremor in comparison with patients receiving placebo, indicating that there may be a pharmacodynamic influence. Patients receiving lithium and sertraline or other substances with a serotonergic mode of action should be appropriately monitored.

Sumatriptan:
In rare cases, weakness, hyperreflexia, lack of coordination, confusion, anxiety and agitation have been reported in association with the concomitant use of sertraline and sumatriptan. Patients in whom it is clinically necessary to administer sertraline and sumatriptan concurrently should be appropriately monitored.

CNS active substances and alcohol:
Concomitant treatment with sertraline 200 mg daily did not increase the effect of alcohol, carbamazepine, haloperidol or phenytoin on psychomotor and cognitive functions in healthy volunteers. However, consumption of alcohol in conjunction with sertraline treatment is not recommended.

Hypoglycaemic substances:
Sertraline may alter glycaemic control. Therefore it is advisable to monitor the blood glucose level when initiating sertraline for diabetic patients. See section 4.4.

Oral anticoagulants, salicylic acid derivates and NSAID:
On concomitant administration of sertraline and warfarin there was a slight, but statistically significant, increase in prothrombin time; close monitoring of prothrombin time is thus advisable when therapy with Sertraline tablets is initiated or terminated (see “active substances bound to plasma proteins” and “Cytochrome P450 interactions / 2C9). There may potentially be an increased risk of bleeding when SSRIs are combined with other oral anticoagulants, salicylic acid derivatives NSAID, atypical antipsychotics, phenothiazines, and most tricyclic antidepressants (see section 4.4).

Diuretics
Diuretics used concomitantly with sertraline may predispose (elderly patients) to hyponatraemia and SIADH.

Medicinal products metabolised by cytochrome P450-enzymes:
CYP 2D6: In interaction studies, there was only a minimal increase in steady-state plasma concentrations of desipramine (23 – 37 % on average) during long term use of sertraline at a dose of 50 mg/day. Desipramine is a marker for cytochrome P450 (CYP) 2D6 isoenzyme activity.
CYP 3A3/4: In vivo interaction studies have shown that long term administration of sertraline at a dose of 200 mg daily does not result in inhibition of CYP 3A3/4mediated 6-β-hydroxylation of endogenous cortisol or metabolism of carbamazepine and terfenadine. There was no inhibition of the CYP 3A3/4-mediated metabolism of alprazolam during long term use of 50 mg/day sertraline. The results of these studies indicate that there is no clinically relevant inhibition of CYP 3A3/4 activity by sertraline.
-CYP 2C9: The lack of any clinically significant effects of long term administration of 200 mg sertraline/day on plasma concentrations of tolbutamide, phenytoin and warfarin shows that sertraline does not inhibit CYP 2C9 to any clinically relevant extent.
CYP 2C19: The lack of any clinically significant effects of long term administration of 200 mg sertraline/day on plasma concentrations of diazepam allows the conclusion that sertraline does not inhibit CYP 2C19 to any clinically relevant extent.
CYP 1A2: In vitro investigations have demonstrated that sertraline has little or no potential for inhibition of CYP 1A2.

Phenytoin:
Although no clinically significant inhibition of the metabolism of phenytoin was observed in a placebo controlled study in healthy subjects, it is advisable to monitor plasma phenytoin concentrations on initiation of sertraline therapy and to adjust the phenytoin dose as appropriate. Concomitant administration of phenytoin can reduce plasma sertraline levels.

Changeover from use of selective serotonin re-uptake inhibitors or other antidepressants: See section 4.4

Antipyrine:
The half-life of antipyrine is reduced by concomitant administration of sertraline, which points to a clinically non-significant hepatic enzyme induction.

**4.6 Pregnancy and lactation**

Pregnancy
Data on a limited number (n = 147) of exposed pregnant women indicate no undesirable effects of sertraline on pregnancy or on the health of the foetus. Animal studies did not provide any evidence of teratogenic effects of sertraline, however embryotoxicity has been observed (see section 5.3). New born infants should be observed if maternal use of sertraline continues into the later stages of pregnancy, particularly the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the new born infants after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

Sertraline should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Women of childbearing age should use a method of contraception if they are receiving sertraline.

Lactation: Sertraline is known to be excreted in breast milk (milk/plasma-ratio approximately 1.8). Very low or non-detectable plasma concentrations of sertraline have been determined in breastfed infants. Sertraline should only be administered during lactation if the expected benefit outweighs potential risk to the child.

**4.7 Effects on ability to drive and use machines**

If used as recommended, Sertraline may in isolated cases alter reactions to such an extent, that the ability to drive and use machines, or to work in potentially hazardous situations is impaired. This applies particularly on commencement of therapy, change of medication and on concomitant ingestion of alcohol or medicinal products which influence the function of the central nervous system. The patient should be warned not to drive or work in potentially hazardous situations until the individual effects of sertraline are known.

**4.8 Undesirable effects**

| Organ System Disorder | Very common (≥1/10) | Common (≥1/100 and <1/10) | Uncommon (≥1/1000 and <1/100) | Rare (≥1/10000 and <1/1000) |
|---|---|---|---|---|
| Blood and lymphatic system disorders: | | | purpura, altered platelet function, altered haemorrhagic diathesis (with e.g. epistaxis, gastrointestinal haemorrhage or haematuria) | leukopenia, thrombocytopenia |
| Endocrine disorders: | | | | gynecomastia, hyperprolactinaemia, galactorrhoea, hypothyroidism, syndrome of inappropriate ADH secretion |
| Metabolism and nutrition disorders: | | | | hyponatraemia: this remitted on discontinuation of therapy. Isolated cases may have been attributable to syndrome of inappropriate ADH secretion. These undesirable effects have mainly occurred in elderly patients and in patients using diuretics or other medicinal products. Elevated serum cholesterol levels. |
| Psychiatric disorders: | insomnia, somnolence, anorexia: | yawning, agitation, anxiety | euphoria, depressive symptoms, hallucinations, mania, hypomania | loss of libido (in women and men), nightmares, aggressive reactions, psychosis, suicidal thoughts/behaviour (see section 4.4) |
| Nervous system disorders: | tremor, dizziness, dry mouth | headache, motor disorders (including extrapyramidal symptoms, such as hyperkinesia, increased muscle tone, teeth-grinding and impaired gait), paraesthesiae, hypaesthesia, increased sweating | migraine. | involuntary muscle contractions, coma, seizures, psychomotor restlessness/akathisia (see section 4.4), signs and symptoms associated with serotonin syndrome: agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia. In some cases, these symptoms occurred in association with the concomitant use of serotonergic agents |
| Eye disorders: | | impaired vision | mydriasis | |
| Ear and labyrinth disorders: | | tinnitus | | |
| Cardiac disorders: | | chest pain, palpitations | hypertension, syncope, tachycardia | |
| Vascular disorders: | | | peripheral oedema, peri-orbital oedema, | |

| Organ System Disorder | Very common (≥1/10) | Common (≥1/100 and <1/10) | Uncommon (≥1/1000 and <1/100) | Rare (≥1/10000 and <1/1000) |
|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | | bronchospasm |
| Gastrointestinal disorders: | nausea, diarrhoea / loose stool | dyspepsia, obstipation, abdominal pain, vomiting | increased appetite, pancreatitis | |
| Hepatobiliary disorders | | | severe hepatic disorders (including hepatitis, jaundice and liver failure), asymptomatic elevation of serum transaminases (SGOT and SGPT). Alterations to transaminase levels mainly occurred in the initial 9 weeks of treatment and rapidly disappeared after discontinuation of therapy. | |
| Skin and subcutaneous tissue disorders | | skin rash | pruritus, alopecia, erythema multiforme | photosensitivity of skin, urticaria, Quincke's oedema, severe dermal exfoliation e.g. Stevens-Johnson-syndrome and epidermal necrolysis |
| Musculoskeletal, connective tissue and bone disorders: | | | arthralgia | |
| Renal and urinary disorders: | | | urinary incontinence | facial oedema, urinary retention |
| Reproductive system and breast disorders: | sexual disorders (mainly delayed ejaculation in men) | menstrual disorders | | priapism |
| General disorders: | | asthenia, tiredness, hot flushes | indisposition, gain of body weight, loss of body weight, fever | Rare: anaphylactoid reaction, allergic reactions, allergy |
| Investigations: | | | abnormal laboratory values | |

Withdrawal symptoms seen on discontinuation: Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported. Generally these events are mild to moderate and are self-limiting. However, in some patients they may be severe and/or prolonged. It is therefore advised that when treatment with sertraline is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

More than 700 elderly patients (aged >65 years) participated in a clinical study to demonstrate the efficacy of sertraline in this patient group. The types and frequency of undesirable effects in the elderly patients were similar to those in younger patients.

**4.9 Overdose**

Symptoms of overdose

The symptoms of sertraline overdose take the form of serotonin-mediated side-effects such as drowsiness, gastrointestinal disorders (e.g. nausea and vomiting), tachycardia, tremor, agitation and dizziness. Coma has been reported in rare cases.

Toxicity
Available data show that sertraline has a broad safety index on overdose. There are reports of ingestion of up to 13.5 g sertraline alone. Fatality mainly occurred after sertraline intoxication when other medications and/or alcohol were ingested concomitantly. It is thus advisable to take an aggressive approach in the treatment of overdose.

Treatment
There is no known specific antidote to sertraline. The following measures are recommended: ensure airways are free and adequate ventilation and O2 therapy are provided. Administration of activated charcoal, in combination with sorbitol solution or another purgative if necessary, is at least as effective as gastric lavage. Induction of vomiting is not advisable. General monitoring of cardiovascular function is advisable and general supportive measures should be provided. Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be effective in view of the large volume of distribution of sertraline.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.2 Pharmacodynamic properties
Pharmacotherapeutic group: Antidepressants, Selective serotonin reuptake inhibitors

ATC: N06A B06

It is postulated that depressive disorders are associated with a disturbance of 5hydroxytryptamine (serotonin) metabolism in the brain. It has been demonstrated in vitro that sertraline is a potent and selective inhibitor of neuronal reuptake of serotonin: this resulted in a potentiation of the physiological effects of the substance in animal models. Sertraline has only very weak effects on neuronal uptake of norepinephrine and dopamine. At clinically effective doses, sertraline inhibits the uptake of serotonin by human blood platelets.

In animal studies, sertraline has been shown to have no stimulating, sedative or anticholinergic / cardiotoxic effects. In experimental investigations conducted in healthy subjects, sertraline exhibited no sedative potential and did not affect psychomotor performance.

As a result of its selective inhibition of serotonin reuptake, sertraline does not influence catecholamine activity. In addition, sertraline has no affinity for muscarinergic, serotonergic, dopaminergic, histaminergic, benzodiazepine, GABA or adrenergic receptors. As in the case of other clinically effective antidepressants, there was downregulation of the responsiveness of cerebral norepinephrine receptors with long term use of sertraline.

No potential for the misuse or abuse of sertraline is reported from human and animals studies

### 5.2 Pharmacokinetic properties
Absorption:
The pharmacokinetic profile of sertraline is proportional to dose over the range 50 – 200 mg. After single oral daily administration of 50 – 200 mg sertraline for 14 days, peak plasma concentrations were reached after 4.5 – 8.4 hours. On the basis of recovery rates in urine and faeces, it can be estimated that absorption after oral administration is at least 70 %. Bioavailability is reduced by the first pass effect. Concomitant consumption of food does not significantly influence the bioavailability of sertraline tablets.

Distribution:
Plasma protein binding of sertraline is approximately 98 %. Data from animal studies indicate that sertraline has a large volume of distribution. Steady-state concentrations are thus reached after approximately 1 week and sertraline concentrations are doubled compared to plasma levels after initial dose with once daily administration.

Metabolism:

Sertraline and the main metabolite, N-desmethylsertraline both undergo extensive hepatic metabolism. In vitro N-desmethylsertraline exhibits considerably less (by a factor of approximately 20) activity than the parent substance. The metabolite had no effect in in vivo depression models.

It has been demonstrated in in vitro investigations that the metabolism of sertraline is mainly mediated by the CYP 3A4 enzyme, with only limited involvement of CYP 2D6. At the standard dose of 50 mg, sertraline has only limited effects on the CYP 2D6- and CYP 3A4mediated metabolism of other substances.

Excretion:
The mean terminal elimination half-life of sertraline is approximately 26 hours. The half-life of N-desmethylsertraline is 62 – 104 hours, so that plasma concentrations of the metabolite reach the same level as the parent substance.

The metabolites of sertraline and N-desmethylsertraline are eliminated in equal fractions in faeces and urine. Only a small percentage (less than 0.2 %) of unchanged sertraline is recovered in urine.

Elderly:
The pharmacokinetic profile of sertraline in elderly patients is similar to that in younger patients.

Hepatic insufficiency:
For pharmacokinetics of sertraline in patients with cirrhosis see sections 4.2 and 4.4.

**5.3 Preclinical safety data**

Conventional preclinical studies on sertraline did not demonstrate mutagenicity nor carcinogenicity. No teratogenic effects have been observed in studies on reproduction toxicity in rats and rabbits. However, delay of ossification occurred in foetus of rats and rabbits in dosages exceeding the maximal therapeutic dose in humans 2.5- up to 10-fold. Administration of sertraline in rats during the last third of gestation till end of lactation in a dosage exceeding the maximal therapeutic dose in humans 5-fold resulted in an increased number of stillbirths as well as in decreased survival rate and body weight of descendants. It could be demonstrated that lower survival rate of descendants is implicated by intrauterine exposure.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

In the tablet core:
Microcrystalline cellulose
Dibasic calcium phosphate dihydrate
Hydroxypropylcellulose
Sodium starch glycolate (Type A)
Magnesium stearate

In the tablet film-coat:
Opadry white YS-1R-7003
Containing:
Hypromellose
Macrogol
Titanium dioxide (E171)
Polysorbate 80

Opadry clear YS-1R-7006
Containing:
Hypromellose
Macrogol

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**
PVC/PVdC aluminium foil blisters

Pack sizes of 7, 14, 20, 28, 30, 35 49, 50, 50 x 1 (unit dose), 98, 100, 250 and 294 film-coated tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**
No special requirements.

**7. MARKETING AUTHORISATION HOLDER**
Clarendon Pharma Limited
19 King Street, Seagrave
Leicestershire
LE12 7LY
United Kingdom

**8. MARKETING AUTHORISATION NUMBER**
PL 20137/0021

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT.**

# Module 3
# Patient Information Leaflet

*PACKAGE LEAFLET: INFORMATION FOR THE USER*

## *Sertraline 50mg and 100mg Film-coated Tablets*

**(Sertraline)**

**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 ARE AND WHAT THEY ARE USED FOR*

The name of your medicine is Sertraline Film-Coated Tablets. This medicine contains the active substance sertraline hydrochloride which is one of a group of medicines called Selective Serotonin Re-uptake Inhibitors (SSRIs).

Sertraline is used in the treatment of:
- Depressive illnesses (major depressive episodes)

### *2. BEFORE YOU TAKE SERTRALINE FILM-COATED TABLETS*

**Do not take Sertraline Film-Coated Tablets**
- If you are allergic (hypersensitive) to sertraline hydrochloride or any of the ingredients in the film-coated tablet (see section 6, Further Information)
- If you are taking any medicines called monoamine oxidase inhibitors (MAOIs). These can be used to treat depression (e.g. phenelzine, tranylcypromine or moclobemide) or Parkinson's disease (e.g. selegiline)
- If you are taking a medicine called pimozide for treating a mental disorder.

**Take special care with Sertraline Film-Coated Tablets**
- If you have recently completed treatment with medicines that belong to the group of MAO inhibitors (e.g. for depression). You must wait at least 14 days or, for some MAO inhibitors such as moclobemide you have to wait for 24 hours before you can start taking sertraline unless your doctor has prescribed it otherwise. Ask your doctor before you change from another antidepressant medicine to sertraline. At least two weeks should elapse between discontinuation of Sertraline Film-Coated Tablets and initiation of therapy with any MAO inhibitor.
- If you have or have had one of the following diseases. You must talk to your doctor about these diseases before you take Sertraline Film-Coated Tablets.
  - Bipolar affective disorder (manic episode). If you have a manic episode, contact your doctor immediately. The use of Sertraline Film-Coated Tablets might need to be discontinued.
  - Epilepsy. If you have a fit (seizure), contact your doctor immediately, the use of Sertraline Film-Coated Tablets might need to be discontinued.
  - Diabetes. Treatment with Sertraline Film-Coated Tablets may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.
  - Increased risk of bleeding
  - Schizophrenia
  - Impaired liver function. Your doctor may need to adjust your dosage.
- If you are receiving electroconvulsive therapy (so-called electric shock treatment).
- If you are taking medicines that cause an increased risk of bleeding, e.g. medicines to thin the blood (anticoagulants), atypical antipsychotics and phenothiazines, most tricyclic antidepressants, medicines for pain and inflammation (NSAIDs) or acetylsalicylic acid).
- If you get a high temperature, muscle stiffness or twitching, confusion, irritability and extreme agitation. In these cases, you must contact your doctor immediately as these symptoms may be an indication of the so-called serotonin syndrome. Although this syndrome occurs rarely it may result in potentially life threatening conditions. The use of Sertraline Film-Coated Tablets might need to be discontinued.

Please note:
Like other medicines of this type, sertraline does not lead to relief of symptoms immediately but usually only after a few weeks. Sometimes the symptoms in depression or other mental illnesses can include thoughts of self-injury or suicide. It is possible that these symptoms will persist or worsen until the full antidepressant effect of the medicine occurs. The probability of this occurring is greater if you are a younger adult.

Symptoms such as anxiety, agitation or difficulties in sitting or standing still can also occur in the first weeks of treatment. If you observe these symptoms in yourself, you should talk to your doctor as soon as possible.

In certain cases, it can happen that you are unaware of the symptoms listed above; it can therefore be of benefit to ask someone close to you to help you to watch yourself for possible different signs.

If you have thoughts of harming or killing yourself or if any of the symptoms listed above occurs during treatment, please contact your doctor or go to a hospital straight away.

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. 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.

**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.

The following medicines can affect or be affected by treatment with Sertraline Film-Coated Tablets:
- MAO inhibitors (for depression or Parkinson's disease) must not be used with Sertraline Film-Coated Tablets as serious or even fatal reactions (serotonin syndrome) can occur (see section "Do not take Sertraline Film-Coated Tablets).
- Pimozide (e.g. for Tourette syndrome) must not be used with Sertraline Film-Coated Tablets.
- Tryptophan, fenfluramine, dextromethorphan, pethidine, tramadol and other SSRIs. Concomitant administration of Sertraline Film-Coated Tablets with these medicinal products should only take place with great caution and, if possible be avoided due to the risk of serotonin syndrome (see "Take special care with Sertraline Film-Coated Tablets")
- Diazepam (a sedative)
- Tolbutamide (for diabetes)
- Cimetidine (for heartburn and stomach ulcers)
- Warfarin (blood thinning medicine)
- Medicines for pain and inflammation (NSAIDs) or acetylsalicylic acid
- Phenazone (for pain)
- Lithium (for manic-depressive illness)
- Diuretics (water tablets)
- Phenytoin (for epilepsy). Because sertraline may influence the blood levels of this drug, your doctor may need to introduce phenytoin more carefully and to adjust the phenytoin dose as appropriate. Phenytoin can reduce the blood levels of sertraline.
- Sumatriptan and other triptans (for migraine)
- Herbal remedies containing St. John's wort (Hypericum perforatum)

**Taking Sertraline Film-Coated Tablets with food and drink**
During treatment with sertraline, consumption of alcohol is not recommended. Sertraline Film-Coated Tablets can be taken with or without food.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy
There is only limited experience concerning the use of sertraline during pregnancy. The benefits of treatment during pregnancy should be carefully weighed against possible risks to the unborn child. Do not take Sertraline Film-Coated Tablets if you are pregnant or planning to become pregnant unless specifically directed by your doctor.

You should not discontinue treatment with Sertraline Film-Coated Tablets abruptly. If you are taking Sertraline Film-Coated Tablets in the last 3 months of pregnancy, let your doctor know as your baby might have some symptoms when it is born. These symptoms usually begin during the first 24 hours after the baby is born. They include not being able to sleep or feed properly, trouble with breathing, a blue-ish skin or being too hot or cold, being sick, crying a lot, stiff or floppy muscles, lethargy, tremors, jitters or fits. If your baby has any of these symptoms when it is born, contact your doctor immediately who will be able to advise you.

Breast-feeding
Sertraline passes into breast milk in small amounts. There is a risk of an effect on the baby. If you are taking Sertraline Film-Coated Tablets, talk to your doctor before you start breast-feeding.

**Driving and using machines**
Sertraline can reduce the ability to react in individual cases and lead to dizziness and fatigue. This can alter your ability to react so much, even when used correctly, that the ability to drive, operate machines or work in an unsupported position is impaired. You must therefore be careful until you know how you react to the medicine.

## *3.HOW TO TAKE SERTRALINE FILM-COATED TABLETS*

You should swallow the tablet whole with a drink of water; do not crush or chew it.

Always take Sertraline Film-Coated Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. If necessary the tablets with a break-line may be broken in half.

**Adults:**

Treatment of depression:
The usual dose in the treatment of depression is 50mg, equivalent to 1 Sertaline 50mg Film-Coated Tablet daily. Your doctor may increase the dose in steps of 50mg to a maximum of 200mg daily if necessary.

Other strengths of Sertraline Film-Coated Tablets and other pharmaceutical forms are available.

**Children and adolescents under 18 years of age:**
Sertraline Film-Coated Tablets should not be used in children and adolescents.

**Your doctor should not make changes to your dose more often than once a week.**

You may need to take Sertraline Film-Coated Tablets for up to 2-4 weeks before you start to feel better. Your doctor will want to monitor your progress closely during this period.
- You must keep taking Sertraline Film-Coated Tablets to help you feel better.
- See your doctor before your tablets run out.

In depression the treatment usually lasts 6 months after an improvement has occurred.

**If you take more Sertraline Film-Coated Tablets than you should,** tell your doctor straight away or go to your local hospital casualty department at once. Don't forget to take your tablets or patient information leaflet with you. An overdose can cause sleepiness, nausea, vomiting, a fast heart rate, shaking, agitation and dizziness.

**If you forget to take Sertraline Film-Coated Tablets**
Do not worry. Just take the next tablet at the right time. Do not take a double dose to make up for a forgotten dose. If you have forgotten to take more than one dose, you should contact you doctor.

**If you stop taking Sertraline Film-Coated Tablets**
Do not stop taking your tablets even if you start to feel better unless you have spoken to your doctor. Your doctor will usually advise you to reduce the dose gradually over several weeks.

If you stop taking your tablets suddenly, you may suffer from dizziness, headache, sleeplessness, nausea (feeling sick or being sick), anxiety and agitation.

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 Film-Coated Tablets can cause side effects, although not everybody gets them.

If any of the following occur, you should tell your doctor immediately:

- If you have an allergic reaction. You should tell your doctor immediately if you experience wheezing, difficulty breathing, swelling, rash or itching (especially affecting the whole body).
- If you have a fit (seizure).
- If you have suicidal thoughts or thoughts of self harm after taking this medicine.

If you experience a high temperature, muscle stiffness or twitching, confusion, irritability and extreme agitation, you must contact your doctor immediately as these symptoms may be an indication of the so-called serotonin syndrome. Although this syndrome only occurs rarely, it can be life-threatening. You may need to stop taking Sertraline Film-Coated Tablets.

The following side effects have been reported at the approximate frequencies shown:

Very common (occurs in more than 1 in 10 patients):
- Difficulty sleeping, sleepiness
- Loss of appetite
- Shaking, dizziness
- Dry mouth
- Nausea, diarrhoea
- Impotence, problems with ejaculation.

Common (occurs in more than 1 in 100 patients):
- Heartburn or indigestion
- Chest pain, palpitations (sensations of irregular or forceful beating of the heart)
- Increased sweating, skin rash, hot flushes
- Yawning, headache
- Feeling agitated, feeling anxious.
- Pins and needles, loss of feeling in the body
- Hyperactivity, changes in muscle tone, teeth-grinding, impaired gait (pattern of walking)
- Problems with sight, ringing in the ears
- Constipation, abdominal pain, vomiting
- Irregular periods
- Lethargy, tiredness.

Uncommon (occurs in fewer than 1 in 100 patients):
- Unusual bleeding (including nosebleeds and blood in the urine), unexplained bruising
- Abnormal feeling of well-being, feeling overexcited, manic reactions, depression, hallucinations
- Migraine
- Joint pain
- Dilated pupils in the eye, swelling of the tissues around the eyes
- Swelling in the arms or legs
- Fast heart rate and high blood pressure
- Increased appetite, gain or loss of body weight
- Inflammation of the pancreas, which causes severe pain in the abdomen and back
- Hepatitis (inflammation of the liver), jaundice (yellowing of the skin or whites of the eyes caused by liver problems), liver failure
- Changes in liver and blood test results
- Itching of the skin, a skin rash with red spots that may have clear centres, hair loss
- Urinary incontinence
- General feeling of being unwell, fever.

Rare (occurs in fewer than 1 in 1000 patients):
- Spontaneous production of breast milk, breast enlargement
- Thyroid problems
- Low blood sodium resulting in fits or confusion, mainly occurring in elderly patients and in patients using diuretics (water tablets) or other medicines
- Low levels of white blood cells
- Increased cholesterol levels in the blood
- Loss of sexual desire, continual abnormal erection of the penis
- Nightmares
- Aggression, loss of feeling of identity, feeling suicidal, psychosis (personality changes which may include hallucinations or delusions)
- Seizures
- Coma
- Problems with movement (such as feeling restless), involuntary muscle contractions
- A condition called serotonin syndrome (feeling agitated, confused, sweating, diarrhoea, fever, high blood pressure, increased heart beat, stiffness)
- Difficulty in breathing or wheezing
- Sensitivity to light, nettle rash, development of large wheals on the skin, severe skin reactions such as Stevens-Johnson syndrome (serious illness with blistering of the skin, mouth, eyes and genitals) and epidermal necrolysis (skin appears as if it has been scalded)
- Swelling of the face
- Difficulty passing water.

**When you stop taking the tablets you may experience withdrawal effects such as dizziness, sensory disturbances (including 'pins and needles' and electric shock sensations), sleep disturbances (including insomnia and intense dreams), feeling agitated, anxious, irritable or confused, shaking, nausea and/or vomiting, sweating, diarrhoea, palpitations, emotional instability and visual disturbances. These should disappear within a few days.**

**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.**

## *5. HOW TO STORE SERTRALINE FILM-COATED TABLETS*

Keep out of the reach and sight of children

Do not use this medicine after the expiry date which is stated on the blister and the outer carton after "EXP". The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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 contain**
- The active substance is sertraline. Each film-coated tablet contains 50mg or 100mg sertraline (as sertraline hydrochloride)
- The other ingredients are:

Tablet core: microcrystalline cellulose, dibasic calcium phosphate dihydrate, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate,
Film coat: hypromellose, macrogol, titanium dioxide (E171) and polysorbate 80.

**What Sertraline Film-Coated Tablets look like and the contents of the pack**
Sertraline Film-Coated tablets are film-coated tablets
The tablets are white, oblong, biconvex film-coated tablets.
The 50mg tablets are marked "SR50" one side with a breakline "|" on the other.
The 100mg tablets are marked "SR100" one side and are blank on the other.

Sertraline Film-Coated Tablets are available in blisters of 7, 14, 20, 28, 30, 35, 49, 50, 50 x 1 (unit dose), 98, 100, 250 and 294 tablets. Not all pack sizes will be marketed.

**Marketing Authorisation Holder**
Clarendon Pharma Limited
19 King Street, Seagrave, Leicestershire LE12 7LY, United Kingdom

**Manufacturer**
Arrow Pharma (Malta) Limited
62 Hal Far Industrial Estate, Birzebbugia BBG06, Malta

This leaflet was last approved in MM/YYYY.

LET009AC

# Module 4

# Labelling

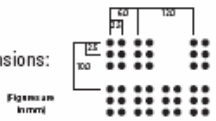

Braille text reads as follows in English:

s e r t r a l i n e # 5 0

m g f i l m - c o a t e d

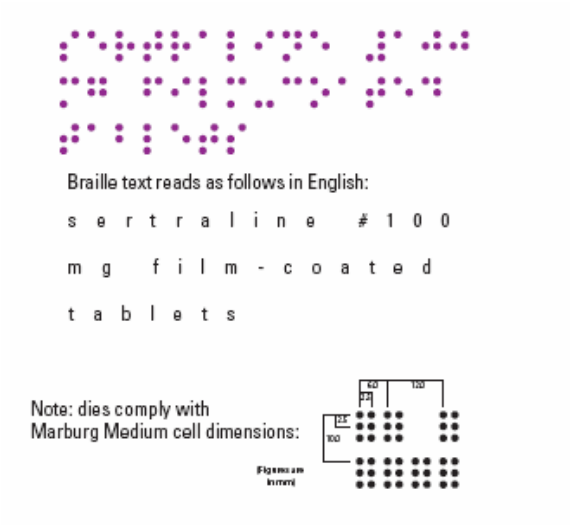
t a b l e t s

Note: dies comply with Marburg Medium cell dimensions:




Sertraline 50mg Tablets
(sertraline) PL 20137/0020 Clarendon Pharma Limited
Sertraline 50mg Tablets (sertraline) PL 20137/0020 Clarendon Pharma Limited
Sertraline 50mg Tablets
(sertraline) PL 20137/0020 Clarendon Pharma Limited


Sertraline 100mg Film-coated Tablets
28 film-coated tablets
Sertraline 100mg Film-coated Tablets
(sertraline)
28 film-coated tablets
Each film-coated tablet contains 100mg sertraline
(as sertraline hydrochloride)
Sertraline 100mg Film-coated Tablets
28 film-coated tablets
arrow generics



Braille text reads as follows in English:

s e r t r a l i n e # 1 0 0

m g f i l m - c o a t e d

t a b l e t s

Note: dies comply with Marburg Medium cell dimensions:



# 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 in the treatment of depressive illness including accompanying symptoms of anxiety, could be approved. A national marketing authorisation was granted on 27/10/2005.

These Mutual Recognition Procedure applications are for Sertraline tablets and are made under EC Article 10.1 of the Directive 2001/83/EC, so called generic applications and are a generic medicinal product to the originator products, Zoloft 50mg Tabletter and Zoloft 100mg Tabletter first licensed in Denmark on 2nd July 1993. Hence the 10-year rule is complied with. The UK reference product is Lustral PL 00057/0308-9.

**About the product**

Sertraline hydrochloride is a selective serotonin reuptake inhibitor indicated for use in the treatment of depressive illness, including accompanying symptoms of anxiety.

**The development programme**

The objective of the development programme was to formulate a robust, stable, acceptable formulation of Sertraline 50mg Tablets and Sertraline 100mg Tablets comparable in performance to Zoloft, the reference product for this generic application

**General comments on compliance with GMP, GLP, GCP and agreed ethical principles**

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

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

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.

## SCIENTIFIC OVERVIEW AND DISCUSSION

## QUALITY ASPECTS

### General Information

### Nomenclature

Chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl–1-napthalenamine hydrochloride

CAS registry number: 79559-97-0

Molecular Formula: $C_{17}H_{18}NCl_3$

Molecular Weight: 342.70

### Physio-Chemical properties

Sertraline hydrochloride is a white to off-white crystalline powder, soluble in methanol. It has a specific optical rotation of +39.0 - +42.0° and a melting range of 243 - 250°C. The pH of a 1% water solution was found to be 5.7.

There are no pharmacopoeia monographs for this active. Appropriate specifications have been provided.

Synthesis of the drug substance from the designated starting material 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.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Active sertraline hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated, supporting the re-test period for the active substance.

## Drug Product

### Description and Composition of the Drug product

Other ingredients consists of pharmaceutical excipients, namely Microcrystalline cellulose, Dibasic calcium phosphate dehydrate, Hydroxypropylcellulose, Sodium Starch Glycolate and Magnesium Stearate, OPADRY YS-1R-7003H White, OPADRY YS-1R-7006 Clear, and Water purified.

The excipients are Ph Eur grade, except for the coating materials that are controlled to in-house specifications. Satisfactory specifications and Certificates of Analysis are provided for typical batches of excipients.

### Manufacture

The manufacturing process is adequately summarised and a flow diagram is provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results of chemical and physical testing of the validation batches are satisfactory and show consistency and control in the manufacturing process.

### Finished Product Specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data for tablets manufactured at the proposed manufacturing site demonstrate that the batches comply with the release specification. Satisfactory certificates of analysis are provided for the reference standards.

### Container Closure System

The tablets are packed in transparent or white opaque aluminium/PVC/PVdC blisters. The proposed aluminium foil and the PVC/PVdC films are stated to be suitable for food and pharmaceutical use. In-house specification and certificates of analysis are also provided for the packaging components and are satisfactory. Satisfactory supplier/manufacturer's specifications for the packaging components are provided.

The blister strips are packed in cardboard cartons containing a total of:

• 1, 7, 14, 20, 28, 30, 35, 49, 50, 98, 100, 250, and 294 tablets.

Deleted: • 1

Deleted: 294 tablets

### Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 year has been set, with no specific storage instructions.

### CONCLUSIONS

Marketing Authorisations may be granted for these products.

# PRE-CLINICAL ASSESSMENT

These applications are generic medicinal product to Zoloft 50mg Tabletter and Zoloft 100mg Tabletter (Pfizer Limited), which have been licenced within the EEA for over 10 years.

No new preclinical data have been supplied with these applications, however, a preclinical expert report, summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

# CLINICAL ASSESSMENT

## 1. INTRODUCTION

These applications under the Mutual Recognition Procedure are for generic medicinal products to Pfizer's Lustral, PL: 00057/0308-9 which were first granted marketing authorisations in the UK on 19th November 1990. Sertraline 50mg Tablets and Sertraline 100mg Tablets were granted Marketing Authorisations on 21st October 2005 in the UK. Although mention is made in the dossier of Sertraline 25mg Tablet this strength was withdrawn and does not have a UK Marketing Authorisation and is therefore not being considered under the MRP.

## 2. BACKGROUND

Sertraline is an anti-depressant. It is a potent selective inhibitor of neuronal reuptake of serotonin (SSRl), thereby facilitating serotinergic transmission.

## 3. INDICATIONS

These are the same as those for the cross-referred product and are satisfactory.

## 4. DOSE & DOSE SCHEDULE

These are the same as those of the cross-referred product and are satisfactory.

## 5. TOXICOLOGY

No new data are provided and none are required for this application.

## 6. CLINICAL PHARMACOLOGY

The applicant has had carried out a comparative bioavailabilty study. This was a single dose, open label, randomised, cross-over trial comparing 100mg tablets of test and reference product. The two study periods were separated by a two week washout period.

There were no serious adverse events.

Results for plasma sertraline were as follows:

**Summary of Pharmacokinetic date for sertraline**

Pharmacokinetic Variables for LUSTRAL™ (Pfizer) and Sertraline Tablets

| Variable | Lustral | Sertraline | 90% CI |
|---|---|---|---|
| Cmax (ng/ml) | 34.3 | 35.6 | 96.9 - 111 |
| AUC0 - t (ngh/ml) | 910 | 919 | 94.6 - 108 |
| AUC0 - ∞ (ngh/ml) | 900 | 920 | 94.7 - 109 |

C.I.: Confidence Interval(%)

From the available information it would seem that:

The study medication was well tolerated. The results indicate that the test product is equivalent to the reference product with respect to the rate and extent of absorption of sertraline, such that the test and reference products may be considered to be bioequivalent.

**7. EFFICACY**
No new data are provided and none are required for this application.

**8. SAFETY**
No new data are provided and none are required for this application.

**9. EXPERT REPORTS**
The expert report is written by a medically qualified consultant and is satisfactory.

**10. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
This is satisfactory

**11. PATIENT INFORMATION LEAFLET**
This is satisfactory

**12. LABELLING**
The labelling is satisfactory

**13. APPLICATION FORM (MAA)**
The MAA is satisfactory.

**14. D ISCUSSION**
The data presented have shown that the product particulars for Clarendon Pharma's sertraline tablets are essentially the same as those of the cross-referred Lustral 100mg Tablets from Pfizer.

**15. CONCLUSION**
Product licences may be granted for these applications.

## 5. Overall Conclusion

**Quality**
The quality aspects of Sertraline 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.

**Pre-Clinical**
No new pre-clinical data were presented or were required for this type of application.

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

The SPC, PIL and labelling are satisfactory and consistent with that for reference product.

**Benefit/Risk Analysis**
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Sertraline is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.

# Module 5

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| 28/09/2007 | Type II | To update the SPC agreed during MRP and bring the PIL and label in line with the SPC | Approved 06/11/2007 |
| | | | |
| | | | |
| | | | |
| | | | |