Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

SERTRALINE 50MG TABLETS
SERTRALINE 100MG TABLETS

UK/H/0863/001-2/MR
UK Licence No: PL 20532/0070-1

Aurobindo Pharma Limited

LAY SUMMARY

The MHRA granted Aurobindo Pharma Limited Marketing Authorisations (licences) for the medicinal products Sertraline 50mg and 100mg Tablets (PL 20532/0070-71) on 25th October 2005. These applications subsequently underwent a mutual recognition procedure in Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain and Sweden which was completed on 5th September 2006. These are prescription only medicines (POM) that are used for the treatment of major depressive episodes.

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

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

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Module 1

Product Name	Sertraline 50mg and 100mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Sertraline hydrochloride
Form	Tablets
Strength	50mg and 100mg
MA Holder	Aurobindo Pharma Limited, Ares Block, Odyssey Business Park, West End Road, South Ruislip, HA4 6QD
Reference Member State (RMS)	UK
CMS	Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain and Sweden
Procedure Number	UK/H/0863/001-2/MR
Timetable	Day 90 – 5th September 2006

Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Sertraline Aurobindo 50mg film-coated tablets
Sertraline Aurobindo 100mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg sertraline (as sertraline hydrochloride).
Each film-coated tablet contains 100mg sertraline (as sertraline hydrochloride).

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.
White capsule shaped, film coated tablets debossed with 'A' on one side and score line in between '8' and '1' on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

White capsule shaped, film coated tablets debossed with 'A' on one side and '82' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depressive episodes.

4.2 Posology and method of administration

For dosage regimens which are not treatable with this strength another appropriate strength is available.

Adults:
The usual daily dose is 50 mg sertraline. If required, the dose can be increased to 100 mg sertraline daily.

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. (see section 5.2)

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

Children and adolescents:
Sertraline Aurobindo 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 is not recommended in case of severe hepatic impairment as no clinical data are available (see section 4.4).

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.

Method and duration of administration:
Sertraline should be taken once daily, mornings or evenings, with sufficient liquid. The tablets may be taken with or without food.

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 of at least 6 months may be required.

Sertraline Aurobindo 50mg film-coated tablets are for oral use only.
Sertraline Aurobindo 100mg film-coated tablets are for oral use only.

Withdrawal symptoms seen on discontinuation of SSRI
Abrupt discontinuation should be avoided. When stopping treatment with sertraline the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 and 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 to any of the excipients.

Sertraline must not be used concurrently with monoamino oxidase (MAO) inhibitors including selegiline and moclobemide and linezolide, an antibacterial exhibiting MAO-reversible blocking activity (see section 4.4 and 4.5).

Sertraline must not be used concurrently with pimozide (also see section 4.5)

4.4 Special warnings and precautions for use
Use in children and adolescents under 18 years of age
Sertraline Aurobindo 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.

Serotoninergic syndrome:
Cases of serious sometimes fatal reactions have been reported in patients receiving sertraline in combination with a MAO inhibitor (MAOI). Therefore sertraline tablets should not be used concomitantly with MAO inhibitors, including the selective MAO inhibitor selegiline and the reversible MAO inhibitor (RIMA) moclobemide, or with linezolide (see section 4.3). Concomitant use of sertraline with other serotoninergic substances, such as tryptophan, fenfluramine and serotonin agonists is not recommended due to the risk of serious adverse reactions (see section 4.5). Sertraline tablets may be started 14 days after discontinuing treatment with an irreversible MAOI. At least 14 days should elapse after discontinuing Sertraline tablets treatment before starting a MAOI or RIMA.
Accordingly 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.

The main features of the serotoninergic syndrome are hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

For other serotoninergic interactions e.g. dextromethorphan, pethidine, tramadol and other SSRIs see 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 self-harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery.

Prescription of sertraline to patients with other psychiatric conditions might also be associated with an increased risk of suicide-related events.

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 suicidal thoughts and to seek medical advice immediately if these symptoms present.

Akathisia/ psychomotor restlessness

The use of sertraline has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Withdrawal symptoms seen on discontinuation of sertraline

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 20% of patients treated with sertraline.

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 of sertraline" in section 4.2 Posology and Method of Administration).

Activation of mania or 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 or 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.

Convulsive disorders:

During studies on depression epileptic seizures were observed in approximately 0.08 % of the patients treated with sertraline.

As sertraline has not been studied in patients with convulsive disorders, the use of this medicinal product should be avoided in patients with unstable epilepsy and should be administered in patients with controlled stable epilepsy only with careful monitoring. If an epileptic seizure occurs, treatment with sertraline should be discontinued.

Electric convulsive therapy (ECT):

Since there is little clinical experience of concurrent administration of sertraline and ECT, caution is advisable.

Diabetes mellitus:

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 be needed to be adjusted.

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-steroids anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders (also see section 4.5).

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 more sensitive to the undesirable effects of antidepressants. The possibility of hyponaetremia, particularly in the case of co-prescription with medications with potential to cause this abnormality, should be anticipated, especially in the elderly, in cases of under-nutrition and in patients with cirrhosis.

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 (C_{max}) 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 dosage 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 (AUC_{0-24} and C_{max}), 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. However, steady state pharmacokinetics of sertraline have not been adequately studied in this patient population and caution is advised when treating patients with renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of some medications in patients receiving SSRI may lead to a serotoninergic syndrome (see section 4.4).

Contraindicated:
MAO inhibitors:

Sertraline should not be used concomitantly with MAO inhibitors, including the selective MAO inhibitor selegiline and the reversible MAO inhibitor moclobemide. There are reports of serious undesirable effects, in some cases involving fatality, in patients using sertraline concurrently with an MAO inhibitor. In some cases, the symptoms were similar to those seen in so-called serotoninergic syndrome. (also see sections 4.3 and 4.4).

Pimozide:

Increased pimozide plasma 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 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 the concomitant use of sertraline with serotonergic substances, such as tryptophan, fenfluramine, sumatriptan, dextromethorphan, pethidine, tramadol and serotonin agonists is not recommended and should be used only under appropriate monitoring (see section 4.4).

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

There is limited controlled experience regarding the optimal timing of switching from other antidepressant drugs to Sertraline. Care and prudent medical judgement should be exercised when switching, particularly from long-acting agents. The duration of washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established (see section 4.4).

St John's Wort : Concomitant use of the herbal remedy St John's Wort (Hypericum perforatum) in patients receiving SSRIs should be avoided since there is a possibility of serotonergic potentiation and serotoninergic syndrome (see section 4.4).

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.

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. The effects of carbamazepine, haloperidol, phenytoin and alcohol were not potentiated after concomitant administration of sertraline: however, it is advisable not to consume alcohol during therapy with sertraline.

Hypoglycaemic substances:
Sertraline may alter glycemic 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 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).

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 3A3/4-mediated 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:* In long term interaction studies with sertraline 200 mg/day and tolbutamide, phenytoin and warfarin, the results may indicate a possible inhibition of CYP2C9.
- *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.

Lithium and tryptophan:

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. Concomitant use may lead to a serotoninergic syndrome (see section 4.4). There have been other reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of SSRIs with these drugs should be undertaken with caution.

Diuretics:

On concomitant administration of diuretics (especially in elderly) the risk for hyponatremia is increased, as well as the risk for inappropriate secretion of antidiuretic hormone.

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.

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.

Phenazone (antipyrine):

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

Tricyclic antidepressants: Caution may be advised when SSRIs are administered with tricyclic antidepressants leading to an increase in their plasma levels.

4.6 Pregnancy and lactation

Pregnancy:

Data on a limited number (n = 147) of exposed pregnant women indicate no adverse effects of sertraline on pregnancy or on the health of the foetus/neonate. Animal studies did not provide any evidence of teratogenic effects of sertraline, although embryotoxicity has been observed (see section 5.3). Sertraline should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus. However, abrupt discontinuation should be avoided during pregnancy.

If maternal use of Sertraline continues into the later stages of pregnancy, particularly the third trimester, new-born infants should be observed.

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

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 risks 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 medicinal product and on concomitant ingestion of alcohol or medicinal products which influence the function of the central nervous system.

The patient should be warned to drive or work in potentially hazardous situations until the individual effects of sertraline are known.

4.8 Undesirable effects

Assessment of frequencies:

Very common:	≥ 1/10
Common:	≥ 1/100, < 1/10
Uncommon:	≥ 1/1,000, ≤ 1/100
Rare:	≥ 1/10,000, ≤ 1/1,000
Very rare:	≤ 1/10,000
Not known:	Cannot be estimated from the available data

The following undesirable effects have been reported in clinical studies in which repeated doses were given:

Gastrointestinal disorders:
Very common: nausea, diarrhoea/loose stool and dry mouth
Common: dyspepsia

Metabolism and nutrition disorders:
Common: anorexia

Nervous system disorders:
Very common: dizziness, somnolence, tremor

Psychiatric disorders:
Very common: insomnia
Rare: Suicidal thought /behaviour

Reproductive system and breast disorders:
Very common: sexual disorders (mainly delayed ejaculation in men)

Skin and subcutaneous disorders
Common: increased sweating

Spontaneous reports of the following undesirable effects have been received in the post-marketing phase:

General disorders:
Common: asthenia, tiredness, hot flushes
Uncommon: indisposition, gain of body weight, loss of body weight, fever
Rare: anaphylactoid reactions

Blood and lymphatic system disorders:
Uncommon: purpura, hemorrhagic disturbances such as ecchymosis, gastro-intestinal hemorrhage, gynecology hemorrhage, and other cutaneous and mucous hemorrhage
Rare: platelet function change, leucopenia, thrombocytopenia

Endocrine disorders:
Rare: gynaecomastia, hyperprolactinaemia, galactorrhoea, hypothyroidism, syndrome of inappropriate ADH secretion

Skin and subcutaneous tissue disorders:
Common: cutaneous exanthema
Uncommon: pruritus, alopecia
Rare: photosensitivity of skin, Quincke's oedema (angioedema), severe dermal exfoliation (Stevens-Johnson-syndrome and epidermal necrolysis), urticaria

Hepatobiliary disorders:
Uncommon: 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.

Cardiovascular disorders:
Common: chest pain, palpitations
Uncommon: peripheral oedema, hypertension, periorbital oedema, syncope, tachycardia

Investigations:
Rare: abnormal laboratory values (e.g. liver function tests, hyponatraemia- see also under blood disorders etc)

Gastrointestinal disorders:
Common: constipation, abdominal pain, vomiting
Uncommon: pancreatitis

Ear and labyrinth disorders:
Common: tinnitus

Nervous system disorders:
Common: headache, motor disorders (including extrapyramidal symptoms, such as hyperkinesia, increased muscle tone, teeth-grinding and impaired gait), paraesthesiae, hypaesthesia
Uncommon: mydriasis, migraine
Rare: Coma, convulsion, involuntary muscle contraction. There have been reported signs and symptoms associated with serotonin syndrome which include agitation, confusion, diaphoresis, diarrhea, fever, hypertension, rigidity and tachycardia. Psychomotor restlessness/akathisia (see section 4.4)

Psychiatric disorders:
Common: yawning, agitation, anxiety
Uncommon: euphoria, depressive symptoms, hallucinations, mania, hypomania
Rare: anorgasmy, incubus nightmares, aggressive reactions, psychosis

Respiratory, thoracic and mediastinal disorders
Rare: bronchospasm

Metabolism and nutrition disorders:
Common: appetite increase
Rare: 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.

Musculoskeletal, connective tissue and bone disorders:
Uncommon: arthralgia

Renal and urinary disorders:
Uncommon: urinary incontinence
Rare: facial oedema, urinary retention

Reproductive system and breast disorders:
Common: menstrual irregularities
Uncommon: priapism

Immune system disorders:
Rare: *allergic reactions, generalized allergy*

Eye disorders:
Common: impaired vision

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 Sertraline treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

The signs and symptoms associated with serotonin syndrome such as agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia, in some cases associated with the concomitant use of serotoninergic medications have also been reported.

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

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

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 medicinal products and/or alcohol were ingested concomitantly. It is thus advisable to take an aggressive approach in the treatment of overdose.

There is no known specific antidote to sertraline. The following measures are recommended: ensure airways are free and adequate ventilation and O_2 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 inhibitor
ATC code: N06AB06

It is postulated that depressive disorders are associated with a disturbance of 5-hydroxytryptamine (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 – 200mg sertraline for 14 days, peak plasma concentrations were reached after 4.5 – 8.4hours.
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 Aurobindo 50mg film-coated tablets/ Sertraline Aurobindo 100mg film-coated 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 3A4-mediated 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 section 4.2 and 4.4.

5.3 Preclinical safety data

In repeated dose toxicity studies, the liver was seen as the main target organ in two animal species studied resulting in increased liver enzyme levels in rats and dogs and centrilobular hepatic hypertrophy at all dose levels in rats.

No teratogenic effects were seen in rats and rabbits. However, delayed ossification occurred in rat and rabbit fetuses at doses 2.5-fold to 10-fold the maximum therapeutic dose in humans. Administration of sertraline to rats during the last third of gestation and until the end of lactation at doses 5-fold the maximum therapeutic dose in humans resulted in an increased number of stillbirths and a reduction in survival and body weight of the offspring. The reduced post-natal survival was shown to be associated with *in utero* rather than post-natal exposure.

On the basis of a standard battery for genotoxicity, sertraline was not shown to be genotoxic.

Carcinogenicity studies showed an increase in the incidence in follicular thyroid adenoma in female rats, lung adenoma in female mice and liver adenoma in male mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablets:

Calcium hydrogen phosphate dihydrate
Cellulose microcrystalline
Hydroxypropylcellulose
Sodium starch glycolate (Type A)
Magnesium stearate

Film coating:

Opadry White OY-S-7355 containing –
Titanium dioxide (E171)
Hypromellose
Macrogol 400
Polysorbate-80

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

White opaque PVC – Aluminium blister or white opaque PVdC – PVC Aluminium blisters

Packs of 10, 14, 28, 30, 42, 50, 56, 84, 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed off in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited,
Ares, Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811.
Fax: ++ 44 20 8845 8795.

8. MARKETING AUTHORISATION NUMBER

To be completed nationally

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sertraline Aurobindo 50 mg film-coated tablets

Sertraline Aurobindo 100 mg 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 Aurobindo is and what it is used for

Sertraline Aurobindo contains the active substance sertraline and are used to treat depression (major depressive episodes).

Sertraline Aurobindo belongs to a group of antidepressant drugs called Selective Serotonin Re-uptake inhibitors.

2) Before you take Sertraline Aurobindo

Do not take Sertraline Aurobindo:
- If you are allergic (hypersensitive) to sertraline or any of the other ingredients of Sertraline Aurobindo.
- If you are taking or if you have recently taken a MAO - inhibitor (MAO- inhibitors are a group of medicines which are for example used for the treatment of depression), including selegiline (for Parkinson's disease), moclobemide (for depression) and Linezolide (a medicine used to treat infection) (See also: Take special care with Sertraline Aurobindo)
- If you are taking Pimozide (a medicine used to treat psychosis)

Take special care with Sertraline Aurobindo:
Use in children and adolescents under 18 years of age : Sertraline Aurobindo 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 Aurobindo for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Sertraline Aurobindo 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 Aurobindo. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Sertraline Aurobindo in this age group have not yet been demonstrated.

Tell your doctor 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 before you can start taking Sertraline Aurobindo unless your doctor has prescribed it otherwise. Ask your doctor before you change from another antidepressant medicine to Sertraline Aurobindo. At least two weeks should elapse between discontinuation of Sertraline Aurobindo and initiation of therapy with any MAO inhibitor.
- 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 Aurobindo might need to be discontinued.
- You have thoughts of harming yourself. People who are depressed can sometimes have thoughts of harming or killing themselves. These may be increased when you first start taking antidepressants, as these medicines take time to work.
- Certain groups of patients may be more likely to think like this:- if you are a young adult aged 18 to 29
- If you have previously had thoughts about killing or harming yourself.

If you get these thoughts at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a friend or relative that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.
- You develop subjectively unpleasant or distressing restlessness and the need to move often accompanied by an inability to sit or stand still (akathisia/psychomotor restlessness). This is most likely to occur within the first few weeks of treatment. Increasing the dose of Sertraline Aurobindo may make these feelings worse (see section "Possible side effects").
- You want to stop taking Sertraline Aurobindo. Do not stop taking Sertraline Aurobindo on your own. Your doctor will advise you when to discontinue the treatment. Symptoms such as dizziness, tingling, headache, anxiety and nausea may occur if the treatment is stopped too quickly. These symptoms are generally non-serious and disappear within few days. If you experience symptoms on stopping treatment, contact your doctor (See also: If you stop taking Sertraline Aurobindo).
- You have or have had a manic episode. If you have a manic episode, contact your doctor immediately. The use of Sertraline Aurobindo might need to be discontinued.
- You have schizophrenia. Psychotic symptoms might become aggravated.
- You have ever had an epileptic fit. If you have a fit (seizure) or experience an increase in seizure frequency, contact your doctor immediately, the use of sertraline might need to be discontinued.
- You are being treated with electroconvulsive therapy (ECT).
- You are suffering from diabetes. Your doctor may need to adjust your dose of insulin or other antidiabetic treatment.
- You have any bleeding disorder or you develop bruises or unusual bleeding.
- 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.
- You have had a heart attack recently or if you suffer from instable heart disease. The safety of sertraline has not been examined in this patient population.
- You are old. The pattern and incidence of adverse reactions in the elderly is similar to that in younger patients. The elderly may be, however, often more sensitive to the undesirable effects of antidepressants.
- You have an impaired liver function. Your doctor may need to adjust your dosage. Sertraline Aurobindo is not recommended in case of severe hepatic impairment as no clinical data are available.

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.

An interaction means that medicines used at the same time can influence the effect(s) and/or side effect(s) of each. The following comments may also apply to medicines that you have used any time in the past or are to use in the near future. An interaction can occur during the use of Sertraline Aurobindo with:
- MAO- inhibitors (MAO-inhibitors are a group of medicines which are used for the treatment of depression). Concomitant use will lead to effects such as fever, muscle pain, confusion and irritation (See also: Do not take Sertraline Aurobindo)
- Pimozide (a medicine used to treat psychosis). Sertraline Aurobindo can increase the side effects of pimozide (See also: Do not take Sertraline Aurobindo)
- Lithium used to treat mental illness), tryptophan (dietary supplement), fenfluramine (used to reduce appetite) or any other antidepressants (tricyclic depressants, SSRIs). Side effects of Sertraline Aurobindo may increase if taken alongwith these drugs.
- Diazepam. Sertraline Aurobindo may increase the effect of diazepam.
- Warfarin (blood thinning drug). Sertraline Aurobindo increases the effect of warfarin and hence blood clotting time should be frequently monitored.
- Tolbutamide (drug used to reduce blood sugar levels). Sertraline Aurobindo increases the effect of tolbutamide and hence blood sugar level should be frequently monitored.
- Cimetidine (drug used in increased acidity in stomach). During concomitant use with Sertraline Aurobindo, blood Sertraline levels may be increased and your doctor may need to reduce the dose of sertraline. Once treatment is completed, it may be necessary for your doctor to increase the dose of Sertraline Aurobindo again.
- Sumatriptan (drug used in migraine). Co-administration may lead to weakness, faulty co-ordination, confusion, unrest and excitement.
- Dextromethorphan, tramadol and pethidine (also pain killers) due to the risk of serotonin syndrome (see ' Take special care with Sertraline Aurobindo')
- Acetylsalicylic acid, phenazone or other pain killers known as NSAIDs (Non-Steroidal Anti-inflammatory drugs) There is increased risk of blood thinning.
- Herbal remedy St. John's Wort (Hypericum perforatum). Possibility of side effects may increase.
- Drugs used in the treatment of diabetes. Concomitant use may alter blood sugar levels. So, blood sugar levels should be monitored more frequently.
- Diuretics (water tablets). Concomitant administration may lead to decrease in blood sodium levels and may affect frequency of urination.
- Phenytoin (for epilepsy). Because Sertraline Aurobindo 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 Aurobindo.

Taking Sertraline Aurobindo with food and drink
You can take Sertraline Aurobindo with or without meals.
Do not consume alcohol during the treatment with Sertraline Aurobindo

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 Aurobindo during pregnancy. The benefits of treatment during pregnancy should be carefully weighed against possible risks to the unborn child. Do not take Sertraline Aurobindo if you are pregnant or planning to become pregnant unless specifically directed by your doctor.

You should not discontinue treatment with Sertraline Aurobindo abruptly. If you are taking Sertraline Aurobindo 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, vomiting, too low sugar content in the blood, 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 Aurobindo passes into breast milk in small amounts. There is a risk of an effect on the baby. If you are taking Sertraline Aurobindo talk to your doctor before you start breast-feeding.

Driving and using machines
Sertraline Aurobindo 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.

You must consult your doctor if you intend to drive or use machinery while taking Sertraline Aurobindo.

3) How to take Sertraline Aurobindo

Always take Sertraline Aurobindo exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose of Sertraline Aurobindo is 50 mg once daily. Doctors may recommend you a higher dose upto a maximum of 200 mg daily. 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.
Your doctor will determine the dose that is most suitable for you. Sertraline Aurobindo is also available in 100 mg/50 mg strength.

Swallow the tablets with a drink of water. Do not crush or chew your tablets. It is best to take them at the same time each day with or without a meal. Keep taking your tablets everyday.

You may need to take Sertraline Aurobindo for up to 2-4 weeks before you start to feel better. Your doctor will want to monitor your progress closely during this period. In depression, the treatment usually lasts 6 months after an improvement has occurred.

You must keep taking Sertraline Aurobindo to help you get better. The treatment with this kind of medication is necessarily long. Your doctor will inform you of how long you will have to take Sertraline Aurobindo. See your doctor before your tablets run out. Even if you begin to feel better, keep taking your tablets. You may need to keep taking them to stay well.

Patients with impaired liver function
In case of impaired liver function, it is recommended that the dose is reduced or the interval between the doses prolonged.

Use in the elderly
The dosage should be as low as possible in the elderly.

If you take more Sertraline Aurobindo than you should
Too many tablets at once can be dangerous. If you take too many tablets tell your doctor. If you are unable to contact your doctor, go to your local hospital casualty department at once. The following effects may appear if you take too many Sertraline Aurobindo: sleepiness, nausea, vomiting, rapid heartbeat, tremor, excitement and dizziness. Less frequently reported was coma.

If you forget to take Sertraline Aurobindo
If you forget to take your medicine, do not worry and take the next dose at the right time. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Sertraline Aurobindo
Do not stop taking Sertraline Aurobindo on your own. Your doctor will advise you when to discontinue the treatment.

Withdrawal symptoms may occur after sudden discontinuation of the treatment with Sertraline Aurobindo. These symptoms include nausea, vomiting, diarrhoea, headache, agitation, anxiety, irritability, sensory and sleep disturbances, confusion, sweating, dizziness, tingling sensation, accelerated heart rate, visual disturbance and emotional instability. The symptoms of withdrawal usually occur within the first few days after the discontinuation of the treatment and usually disappear within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). Talk to your doctor about gradually reducing the dose. If you experience symptoms on stopping treatment, contact your doctor.

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 Aurobindo can cause side effects, although not everybody gets them. The frequency of the side effects can be classified as follows :

Very common : affecting more than 1 out of 10 patients treated
Common : affecting more than 1 out of 100 patients and less than 1 out of 10 patients treated
Uncommon: affecting more than 1 out of 1000 patients and less than 1 out of 100 patients treated
Rare: affecting more than 1 out of 10000 patients and less than 1 out of 1000 patients treated

The following undesirable effects have been reported in clinical studies in which repeated doses were given:

Gastrointestinal disorders:
Very common: nausea, diarrhoea/loose stool and dry mouth
Common: indigestion (dyspepsia)

Metabolism and nutrition disorders:
Common: loss of appetite (anorexia)

Nervous system disorders:
Very common: dizziness, excessive sleepiness (somnolence), tremor (shaky feeling)

Psychiatric disorders:
Very common: insomnia (not being able to sleep)
Rare: suicidal thought /behaviour

Reproductive system and breast disorders:
Very common: sexual disorders (mainly delayed ejaculation in men)

Skin and subcutaneous disorders
Common: increased sweating

Spontaneous reports of the following undesirable effects have been received in the post-marketing phase:

General disorders:
Common: weakness, tiredness, hot flushes
Uncommon: indisposition, gain of body weight, loss of body weight, fever
Rare: severe allergic reactions (anaphylactoid reactions)

Blood and lymphatic system disorders:
Uncommon: purpura (bleeding of skin or mucous membranes (such as lining of the mouth) hemorrhagic disturbances such as ecchymosis (bleeding of skin or mucous membranes), gastro-intestinal hemorrhage, gynaecological haemorrhage, and other cutaneous and mucous haemorrhages.
Rare: decrease in blood platelets which are blood cells responsible for blood clotting (thrombocytopenia), altered platelet function, decrease in white blood cell leading to increased sensitivity to infections (leucopenia),

Endocrine disorders:
Rare: breast enlargement in men (gynaecomastia), abnormal production of breast milk (hyperprolactinaemia), persistent secretion of milk (galactorrhoea), lack of thyroid gland function (hypothyroidism), decreased secretion of antidiuretic hormone due to which frequency of urination increases (syndrome of inappropriate ADH secretion)

Skin and subcutaneous tissue disorders:
Common: widespread rash (cutaneous exanthema)
Uncommon: itching (pruritus), loss of hair (alopecia)
Rare: allergic reaction to light (photosensitivity of skin), Quincke's oedema (oedema of the lips, eyelids and genitalia. Tongue and larynx may also be affected), itching with high fever, red spots on the skin of the hands, joints and eyelids (Stevens-Johnson-syndrome), blister formation (epidermal necrolysis), urticaria (a temporary skin condition similar to nettle rash).

Hepatobiliary disorders:
Uncommon: severe hepatic disorders including swelling of the liver (hepatitis) associated with jaundice (yellow color of skin or eyes) and liver failure, elevation or alteration of liver enzymes

Cardiovascular disorders:
Common: chest pain, rapid heart beat (palpitations)
Uncommon: swelling in the body (peripheral oedema), increased blood pressure (hypertension), swelling around the eye socket (periorbital oedema), sudden unconsciousness which can last from seconds to minutes (syncope), accelerated heart beat (tachycardia)

Investigations:
Rare: abnormal laboratory values

Gastrointestinal disorders:
Common: constipation, abdominal pain, vomiting
Uncommon: inflammation of pancreas (pancreatitis)

Ear and labyrinth disorders:
Common: ringing sound in the ears (tinnitus)

Nervous system disorders:
Common: headache, movement disorders (hyperactivity, increased muscle tone, teeth-grinding and impaired gait), tingling sensation (paraesthesia), decreased sensitivity to touch and pain (hypaesthesia)
Uncommon: abnormal dilation of pupils (mydriasis), migraine
Rare: Coma, convulsion, involuntary muscle contraction. There have been reported signs and symptoms associated with serotonin syndrome which include unrest (agitation), confusion, sweating (diaphoresis), diarrhea, fever, hypertension, rigidity and accelerated heart beat (tachycardia). Inability to sit still or remain motionless (psychomotor restlessness/akathisia)

Psychiatric disorders:
Common: yawning, agitation, anxiety
Uncommon: euphoria, depressive symptoms, observation of things that are not there (hallucinations), mania or hypomania (persistent hyperactivity, intense enthusiasm or violent abnormal behavior)
Rare: failure to experience an orgasm, nightmares, aggressive reactions, serious mental illness including possible change of personality, loss of contact with reality, delusions and/or hallucinations (psychosis)

Respiratory, thoracic and mediastinal disorders:
Rare: difficulty in breathing

Metabolism and nutrition disorders:
Common: appetite increase
Rare: decreased sodium level in the blood (hyponatraemia), elevated serum cholesterol levels

Musculoskeletal, connective tissue and bone disorders:
Uncommon: joint pain (arthralgia)

Renal and urinary disorders:
Uncommon: difficulty to stop passage of urine (urinary incontinence)
Rare: swelling of the face (facial oedema), inability to pass urine (urinary retention)

Reproductive system and breast disorders:
Common: menstrual irregularities
Uncommon: continuous painful erection (priapism)

Immune system disorders:
Rare: allergic reactions, generalized allergy

Eye disorders:
Common: impaired vision

If Sertraline Aurobindo is discontinued, withdrawal symptoms such as excitement, unrest (agitation), fear, dizziness, headache, nausea and tingling sensation (parasthesia) may be experienced.

Most undesirable effects are usually mild and tend to wear off as you take the tablets for longer. If they cause you discomfort or are long lasting, check with your doctor or pharmacist.

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

5) How to store Sertraline Aurobindo

Keep out of the reach and sight of children.

Do not use Sertraline Aurobindo after the expiry date which is stated on the blister after EXP and on the carton after Expiry Date. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.
Store in the original package.
Do not use Sertraline Aurobindo if you notice visible signs of deterioration.

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

6) Further information

What Sertraline Aurobindo contains
The active substance is Sertraline.

Sertraline Aurobindo 50 mg film-coated tablets
Each film-coated tablet contains 50 mg sertraline (as sertraline hydrochloride).

Sertraline Aurobindo 100 mg film-coated tablets
Each film-coated tablet contains 100 mg sertraline (as sertraline hydrochloride)

The other ingredients are:

Core:
Cellulose microcrystalline, Sodium starch glycolate (Type A), Hydroxypropylcellulose, Calcium hydrogen phosphate dihydrate, Magnesium stearate.

Coating:
Hypromellose, Macrogol 400, Polysorbate 80 and Titanium dioxide (E171).

What Sertraline Aurobindo look like and contents of the pack
Film-coated tablets.

Sertraline Aurobindo 50 mg film-coated tablets are white capsule shaped, film-coated tablets marked with 'A' on one side and with a score line between '8' and '1' on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Sertraline Aurobindo 100 mg film-coated tablets are white capsule shaped, film-coated tablets marked with 'A' on one side and '82' on the other side.

Sertraline Aurobindo 50 / Sertraline Aurobindo 100 mg film-coated tablets are available in packs of 10, 14, 28, 30, 42, 50, 56, 84 and 100 film-coated tablets. Not all pack sizes may be marketed.

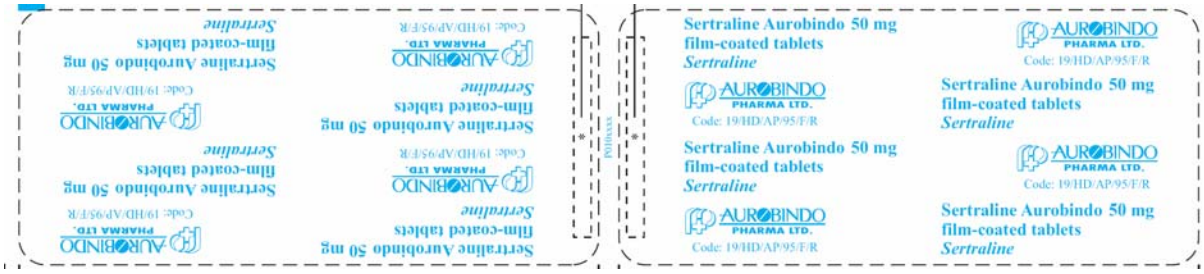
Marketing Authorisation Holder
Aurobindo Pharma Limited,
Ares, Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811.
Fax: ++ 44 20 8845 8795.

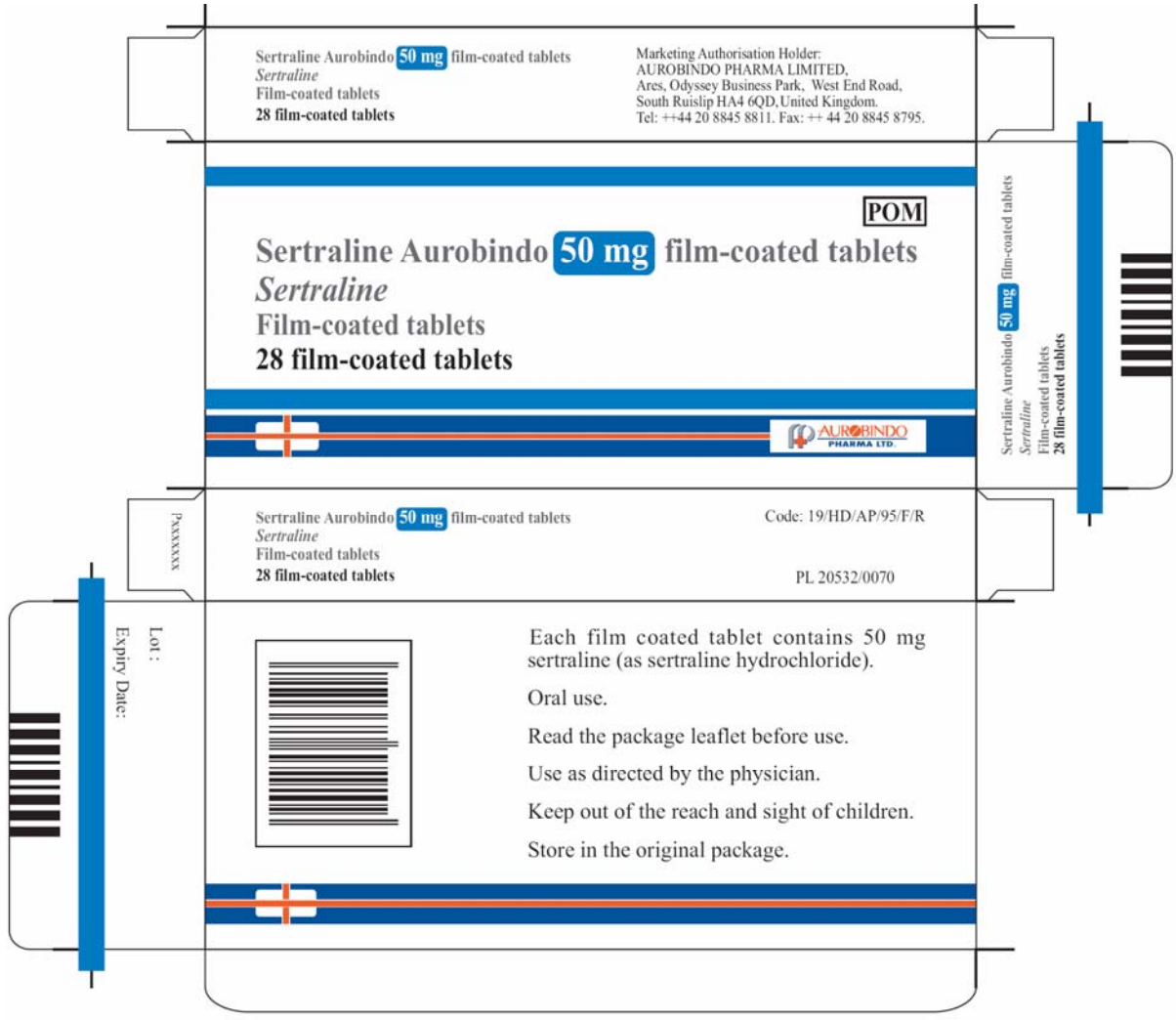
Manufacturer
Aurex Generics Limited,
Ares, Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811.
Fax: ++ 44 20 8845 8795.

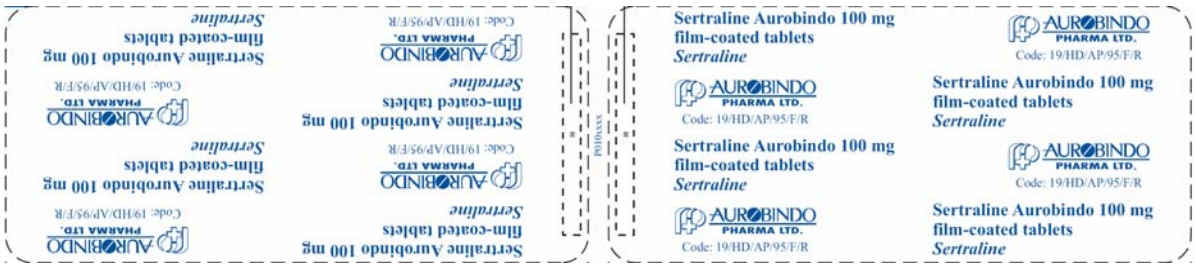
This leaflet was last approved in {MM/YYYY}

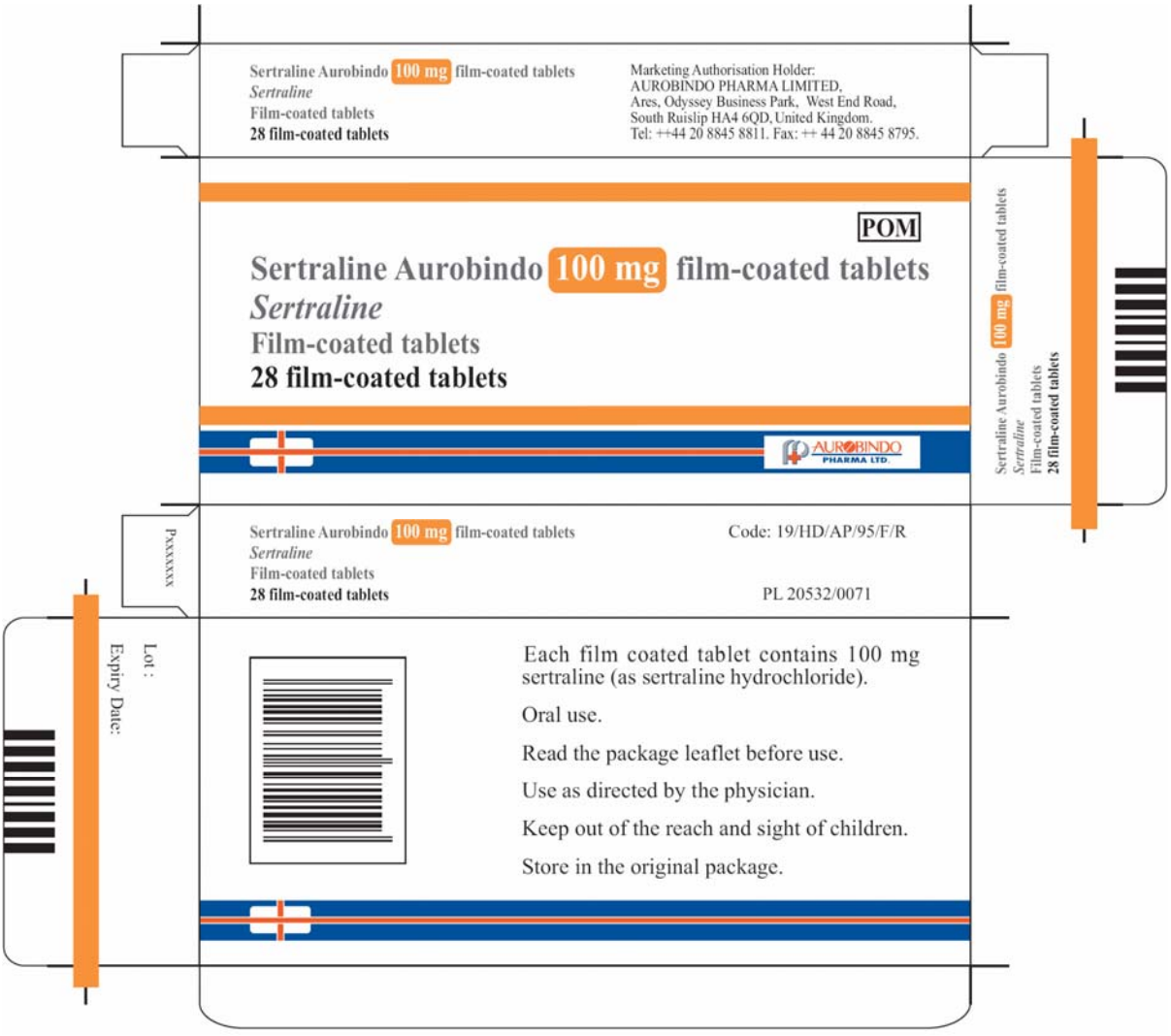
Module 4

Labelling






Sertraline Aurobindo 100 mg
film-coated tablets
Sertraline
AUROBINDO PHARMA LTD.
Code: 19/HD/AP/95/F/R
PXXXXXX


Sertraline Aurobindo 100 mg film-coated tablets
Sertraline
Film-coated tablets
28 film-coated tablets
Marketing Authorisation Holder:
AUROBINDO PHARMA LIMITED,
Ares, Odyssey Business Park, West End Road,
South Ruislip HA4 6QD, United Kingdom.
Tel: ++44 20 8845 8811. Fax: ++ 44 20 8845 8795.
POM
Sertraline Aurobindo 100 mg film-coated tablets
Sertraline
Film-coated tablets
28 film-coated tablets
AUROBINDO PHARMA LTD.
Sertraline Aurobindo 100 mg film-coated tablets
Sertraline
Film-coated tablets
28 film-coated tablets
PXXXXXX
Sertraline Aurobindo 100 mg film-coated tablets
Sertraline
Film-coated tablets
28 film-coated tablets
Code: 19/HD/AP/95/F/R
PL 20532/0071
Lot :
Expiry Date:
Each film coated tablet contains 100 mg sertraline (as sertraline hydrochloride).
Oral use.
Read the package leaflet before use.
Use as directed by the physician.
Keep out of the reach and sight of children.
Store in the original package.

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

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

National marketing authorisations were granted to Aurobindo Pharma Limited for the medicinal products Sertraline 50mg and 100mg Tablets (PL 20532/0070-1) on 25th October 2005. These applications subsequently underwent a mutual recognition procedure in Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain and Sweden which was completed on 5th September 2006.

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

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

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

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

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

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

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Sertraline 50mg Tablets Sertraline 100mg Tablets
Name(s) of the active substance(s) (INN)	Sertraline Hydrochloride
Pharmacotherapeutic classification (ATC code)	Nervous system – psychoanaleptics (NO6 AB06)
Pharmaceutical form and strength(s)	50mg and 100mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/0863/01-02/MR
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain and Sweden
Marketing Authorisation Number(s)	PL 20532/0070-1
Name and address of the authorisation holder	Aurobindo Pharma Limited, Ares Block, Odyssey Business Park, West End Road, South Ruislip, HA4 6QD

III SCIENTIFIC OVERVIEW AND DISCUSSION

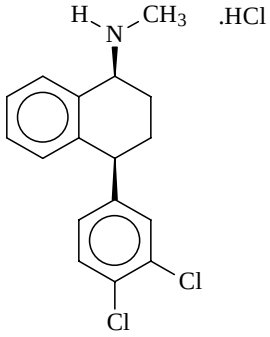
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Sertraline Hydrochloride

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

Structural formula:



Molecular formula: $C_{17}H_{17}Cl_2N$, HCl

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

Molecular weight: 342.73

Sertraline has no European Pharmacopoeia monograph.

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

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

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

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

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. A suitable retest period has been set based on this data.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, sodium starch glycollate, hydroxypropylcellulose, water purified, calcium hydrogen phosphate dihydrate, magnesium stearate and Opadry OY-S-7335 White (macrogol 400, polysorbate 80, titanium dioxide and hypromellose).

All excipients comply with their European Pharmacopoeia monograph, with the exception of Opadry OY-S-7335 White (which is controlled to suitable in-house specifications).

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

Pharmaceutical development

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

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

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

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

Manufacturing Process

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

Finished Product Specification

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

Container-Closure System

Both strengths of tablets are packaged in white opaque polyvinylchloride/aluminium or polyvinylidene chloride/polyvinylchloride/aluminium blisters in pack sizes of 10, 14, 28, 30, 42, 50, 56, 84 and 100 film-coated tablets.

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

Stability of the product
Stability studies were performed on batches of all strengths of finished product and in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies were within specified limits. These data support a shelf-life of 2 years with the storage condition 'Store in original package'.

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

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

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

MAA forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
No new preclinical data have been supplied with these applications and none are required for applications of this type.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
With the exception of the bioequivalence study comparing the proposed 100mg product to Lustral 100mg Tablets, no formal data are provided and none are required for these applications.

A randomised, single-dose, two-way, crossover study was performed comparing the proposed 100mg product (Test) versus Lustral 100mg Tablets (Reference) in healthy fasted volunteers. Blood samples were taken pre- and up to 144 hours post dose, with a washout period of 14 days.

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

Results from this study are presented below:

Parameter	**Arithmetic Mean ± SD (range)**		**Mean ratios (%)**
	Reference Product	Test Product	
C_{max} ng/ml	29.75 ± 9.8 (12.22-52.11)	30.25 ± 9.6 (12.85-49.24)	101.7
T_{max} h	7.71 ± 2.2 (6.00-16.00)	7.75 ± 1.9 (4.00-11.00)	
$AUC_{(0-t)}$ ng.h/ml	1107.8 ± 424.7 (538.23-2196.43)	1130.9 ± 370.6 451.55-2069.88)	102.1
$AUC_{(0-\alpha)}$ ng.h/ml	1166.9 ± 461.8 (562.90-2370.62)	1191.0 ± 406.0 476.77-2239.94)	102.1
$\frac{AUC_{(0-t)}}{AUC_{(0-\alpha)}}$	94.9 %	95.0 %	
$t_{1/2}$ h	30.45 ± 5.6 (20.29-41.28)	30.16 ± 6.6 (13.03-42.44)	

Parameter	**Geometric Mean**		**Mean ratio (%)**	**90% CI**	**Intra-subject CV (%)**
	Reference Product	Test Product			
C_{max} ng/ml	28.183	28.746	102.00	93.56 – 111.20	17.56
$AUC_{(0-t)}$ ng.h/ml	1030.99	1070.62	103.84	98.04 – 109.99	11.65
$AUC_{(0-\alpha)}$ ng.h/ml	1082.82	1123.68	103.77	98.17 – 109.70	11.24

The 90% confidence intervals fall within the currently acceptable range of 80 to 125%, showing bioequivalence between the two products.

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

Efficacy

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

Safety

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

SPC, PIL, Labels

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

Conclusion

The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

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

PRECLINICAL

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

EFFICACY

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

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT

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

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
05/06/2006	Ib	To add Almus Pharmaceuticals, Alliance House, 2 Heath Road, Weybridge, Surrey Kt13 8AP as an own label supplier of the product. Changes to the artwork text that relate to this variation is included.	Approved 11/10/2006
27/04/2007	Ia	To change the address of the Marketing Authorisation Holder, Aurobindo Pharma Limited, from Centurion House, 65 Delamere Road, Hayes, Middlesex, UB4 0NN, United Kingdom to Ares, Odyssey Business Park, West End Road, South Ruislip, HA4 6QD, United Kingdom, with consequential changes to section 7 of the SPC, labels and PIL.	Approved 08/05/2007
30/07/2007	Ib	To register a change of the Aurex Generics Limited batch release site address from Centurion House, 65 Delamere Road, Hayes, Middlesex, UB4 0NN, United Kingdom, to Ares, Odyssey Business Park, West End Road, South Ruislip, HA4 6QD, United Kingdom. The PIL has been updated to reflect the change.	Approved 07/09/2007