Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Sertraline 50mg Film-Coated Tablets

Sertraline 100mg Film-Coated Tablets

UK/H/861/001-2

TEVA UK Limited

Lay Summary

Austria, Belgium, the Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, The Netherlands, Poland, Portugal, the Slovak Republic, Slovenia and Sweden granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Sertraline 50 mg and 100 mg Film-coated Tablets (Product Licence numbers: PL 00289/0560 and 00289/0561). These medicines are available by prescription only.

Sertraline tablets are used to treat depression, obsessive compulsive disorder (OCD) or post traumatic stress disorder (PTSD) in adults. Sertraline is also used to treat OCD in children of six years and older. Sertraline 50 mg and 100 mg Film-coated Tablets contain the active ingredient sertraline hydrochloride, which acts on nerve cells in the brain, helping to control the behaviour associated with depression, OCD or PTSD.

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

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Module 1

Information about initial procedure

Name of the product in the Reference Member State	Sertraline 50 mg Film-coated Tablets Sertraline 100 mg Film-coated Tablets
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial/Additional strength Level 3 Generic, Article 10.1 Level 4 Chemical substance Level 5 Prescription only
Name of the active substance (INN)	Sertraline hydrochloride
Pharmacotherapeutic classification (ATC code)	N06A B06
Pharmaceutical form and strength(s)	Film-coated tablets, 50 mg Film-coated tablets, 100 mg
Reference numbers for the Mutual Recognition Procedure	UK/H/861/001-2
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, The Netherlands, Poland, Portugal, Slovak Republic, Slovenia and Sweden
Date of first authorisation	12 December 2005
Marketing Authorisation Number(s)	PL 00289/0560 PL 00289/0561
Date of assessment report	12 April 2006
Name and address of the authorisation holder	TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK

Module 2

Summary of Product Characteristics

50 mg:

1. NAME OF THE MEDICINAL PRODUCT

Sertraline 50 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg of sertraline (as sertraline hydrochloride).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light blue, film coated elliptical shaped tablet, on one side scored and debossed “9” and “3” from each side of the score. Debossed with “7176” on the opposite side of the tablet.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depressive episodes.

4.2 Posology and method of administration

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. 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.

Children and adolescents:

Sertraline 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).

Method and duration of administration:

Sertraline film-coated tablets are for oral use only.

Sertraline should be taken once daily, mornings or evenings, with sufficient liquid. The tablets may be taken at mealtimes or independently of food intake.

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.

Withdrawal symptoms seen on discontinuation

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 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 to any of the excipients.

Sertraline must not be used concurrently with monoamino oxidase (MAO) inhibitors including selegiline and moclobemide (see section 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 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.

Serotonergic syndrome:

Cases of serious sometimes fatal reactions have been reported in patients receiving sertraline in combination with a MAO inhibitor. Therefore sertraline tablets should not be used concomitantly with MAO inhibitors, including the selective MAO inhibitor selegiline and the reversible MAO inhibitor moclobemide or with other serotonergic substances, such as tryptophan, fenfluramine and serotonin agonists due to the risk of serious adverse reactions (see sections 4.3 and 4.5).

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 the treatment-free interval needed during changeover from one antidepressant to another.

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 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.

Akathisia/psychomotor restlessness:

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

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.

Convulsive disorders:

During studies on depression epileptic seizures were observed in approximately 0.08% of 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:

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.

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, palpitaions, 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 section 4.2 "Withdrawal Symptoms Seen on Discontinuation").

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).

Cardiac disease:

The safety of sertraline has not been established in patients who have recently suffered a heart attack or patients with unstable 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 adverse events 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.

Schizophrenia:

Psychotic symptoms might become aggravated in schizophrenic patients.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 adverse events, 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 serotonin syndrome. An interval of at least 14 days should be observed between termination of MAO inhibitor treatment and initiation of therapy with sertraline. Administration of an MAO inhibitor should be commenced 14 days at the earliest after discontinuation of use of sertraline (also see sections 4.3 and 4.4).
The characteristic symptoms of interaction between a selective serotonin reuptake inhibitor and an MAO inhibitor are hyperthermia, rigor, myoclonus, autonomic disorders which may involve rapid alterations in vital functions, psychological changes such as confusion, irritability and extreme agitation, with delirium and coma in extreme cases.

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 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, serotonin agonists and other SSRIs should not be used concurrently with sertraline (see section 4.4).

Similarly, dextromethorphan, tramadol and pethidine should not be used concurrently with sertraline.

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. 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:
See section 4.4.

Oral anticoagulants, salicylic acid derivates and NSAIDs:
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 "Medicinal products metabolised by cytochrome P450-enzymes – CYP 2C9").

There may potentially be an increased risk of bleeding when SSRIs are combined with other oral anticoagulants, salicylic acid derivatives and NSAID (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:* 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.

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.

Diuretics:

On concomitant administration of diuretics (especially in the elderly) the risk of hyponatremia is increased, as well as the risk of 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.

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 clinically non-significant hepatic enzyme induction.

4.6 Pregnancy and lactation

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 fetus/neonate. Animal studies did not provide any evidence of teratogenic effects of sertraline, however 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 fetus.

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.

Withdrawal symptoms in the neonate after discontinuation of therapy have been reported with sertraline if administered at the end of pregnancy and/or lactation (excitement, agitation, insomnia, sucking weakness).

4.7 Effects on ability to drive and use machines

Sertraline has minor or moderate influence on the 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 not 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 adverse reactions have been reported in clinical studies in which repeated doses were given:

Psychiatric disorders:
Very common: insomnia, somnolence, anorexia

Nervous system disorders:
Very common: tremor, dizziness

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

Renal and urinary disorders:
Very common: sexual disorders (mainly delayed ejaculation in men)

General disorders:
Common: increased sweating

Spontaneous reports of the following adverse events have been received in the post-marketing phase:

Blood and lymphatic system disorders:
Uncommon: purpura, altered platelet function, altered haemorrhagic diathesis (with e.g. epistaxis, gastrointestinal haemorrhage or haematuria)
Rare: leukopenia, thrombocytopenia

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

Metabolism and nutrition disorders:

Rare: hyponatraemia, which remitted on discontinuation of therapy. Isolated cases may have been attributable to syndrome of inappropriate ADH secretion. These adverse events have mainly occurred in elderly patients and in patients using diuretics or other medicinal products. Elevated serum cholesterol levels.

Psychiatric disorders:

Common: yawning, agitation, anxiety

Uncommon: euphoria, depressive symptoms, hallucinations, mania, hypomania

Rare: loss of libido (in women and men), nightmares, aggressive reactions, psychosis, suicidal thoughts / behaviour (see section 4.4)

Nervous system disorders:

Common: headache, motor disorders (including extrapyramidal symptoms, such as hyperkinesia, increased muscle tone, teeth-grinding and impaired gait), paraesthesiae, hypaesthesia

Uncommon: migraine

Rare: psychomotor restlessness / akathisia (see section 4.4), involuntary muscle contractions, coma, seizures, 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:

Common: impaired vision

Uncommon: mydriasis

Ear and labyrinth disorders:

Common: tinnitus

Cardiac disorders:

Common: chest pain, palpitations

Uncommon: hypertension, syncope, tachycardia

Vascular disorders:

Uncommon: peripheral oedema, periorbital oedema

Respiratory, thoracic and mediastinal disorders:

Rare: bronchospasm

Gastrointestinal disorders:

Common: obstipation, abdominal pain, vomiting

Uncommon: increased appetite, pancreatitis

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.

Skin and subcutaneous tissue disorders:

Common: skin rash

Uncommon: pruritus, alopecia, erythema multiforme

Rare: photosensitivity of skin, urticaria, Quincke's oedema, severe dermal exfoliation e.g. Stevens-Johnson syndrome and epidermal necrolysis

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 disorders

Rare: priapism

General disorders:

Common: asthenia, tiredness, hot flushes

Uncommon: indisposition, gain of body weight, loss of body weight, fever

Rare: anaphylactoid reaction, allergic reactions, allergy

Investigations:

Uncommon: 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 sertraline treatment 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 adverse events 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 adverse events 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 inhibitors
ATC code: N06A B06

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 muscarinic, serotonergic, dopaminergic, histaminergic, benzodiazepine, GABA or adrenergic receptors. As in the case of other clinically effective antidepressants, there was down-regulation 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 of once daily dosing; sertraline concentrations are doubled compared to plasma levels after initial dose with once daily administration.

Metabolism:

Sertraline and its 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 section 4.4.

5.3 Preclinical safety data

Conventional studies on sertraline did not demonstrate mutagenicity or carcinogenicity. No teratogenic effects have been observed in studies on reproduction toxicity in rats and rabbits. However, delay of ossification occurred in the fetuses of rats and rabbits in dosages exceeding the maximal therapeutic dose in humans 2.5- up to 10-fold. Administration of sertraline to rats during the last third of gestation and until the 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. The reduced post-natal survival was shown to be associated with *in utero* exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Cellulose, microcrystalline

Calcium hydrogen phosphate dihydrate
Povidone K-30
Croscarmellose sodium
Magnesium stearate
Coating - Opadry
Hypromellose
Titanium dioxide (E171)
Macrogol 6000
Polysorbate 80
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Transparent and white opaque PVC/PVdC aluminium blisters.
Pack sizes: 7, 10, 15, 20, 28, 30, 50, 60, 98, 100, 200, 294 and 300 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8. MARKETING AUTHORISATION NUMBER

PL 00289/0560

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

27 October 2005

10. DATE OF REVISION OF THE TEXT

01/10/2007

100 mg:

1. NAME OF THE MEDICINAL PRODUCT

Sertraline 100 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light yellow, film coated elliptical shaped tablet, on one side scored and debossed "9" and "3" from each side of the score. Debossed with "7177" on the opposite side of the tablet.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depressive episodes.

4.2 Posology and method of administration

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. 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.

Children and adolescents:

Sertraline 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).

Method and duration of administration:

Sertraline film-coated tablets are for oral use only.

Sertraline should be taken once daily, mornings or evenings, with sufficient liquid. The tablets may be taken at mealtimes or independently of food intake.

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.

Withdrawal symptoms seen on discontinuation

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 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 to any of the excipients.

Sertraline must not be used concurrently with monoamino oxidase (MAO) inhibitors including selegiline and moclobemide (see section 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 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.

Serotonergic syndrome:

Cases of serious sometimes fatal reactions have been reported in patients receiving sertraline in combination with a MAO inhibitor. Therefore sertraline tablets should not be used concomitantly with MAO inhibitors, including the selective MAO inhibitor selegiline and the reversible MAO inhibitor moclobemide or with other serotonergic substances, such as tryptophan, fenfluramine and serotonin agonists due to the risk of serious adverse reactions (see sections 4.3 and 4.5).

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 the treatment-free interval needed during changeover from one antidepressant to another.

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 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.

Akathisia/psychomotor restlessness:

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

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.

Convulsive disorders:

During studies on depression epileptic seizures were observed in approximately 0.08% of 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:

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.

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 section 4.2 "Withdrawal Symptoms Seen on Discontinuation").

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).

Cardiac disease:

The safety of sertraline has not been established in patients who have recently suffered a heart attack or patients with unstable 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 adverse events 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.

Schizophrenia:

Psychotic symptoms might become aggravated in schizophrenic patients.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 adverse events, 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 serotonin syndrome. An interval of at least 14 days should be observed between termination of MAO inhibitor treatment and initiation of therapy with sertraline. Administration of an MAO inhibitor should be commenced 14 days at the earliest after discontinuation of use of sertraline (also see sections 4.3 and 4.4).
The characteristic symptoms of interaction between a selective serotonin reuptake inhibitor and an MAO inhibitor are hyperthermia, rigor, myoclonus, autonomic disorders which may involve rapid alterations in vital functions, psychological changes such as confusion, irritability and extreme agitation, with delirium and coma in extreme cases.

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 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, serotonin agonists and other SSRIs should not be used concurrently with sertraline (see section 4.4).

Similarly, dextromethorphan, tramadol and pethidine should not be used concurrently with sertraline.

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. 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:
See section 4.4.

Oral anticoagulants, salicylic acid derivates and NSAIDs:
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 "Medicinal products metabolised by cytochrome P450-enzymes – CYP 2C9").

There may potentially be an increased risk of bleeding when SSRIs are combined with other oral anticoagulants, salicylic acid derivatives and NSAID (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:* 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.

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.

Diuretics:

On concomitant administration of diuretics (especially in the elderly) the risk of hyponatremia is increased, as well as the risk of 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.

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 clinically non-significant hepatic enzyme induction.

4.6 Pregnancy and lactation

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 fetus/neonate. Animal studies did not provide any evidence of teratogenic effects of sertraline, however 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 fetus.

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.

Withdrawal symptoms in the neonate after discontinuation of therapy have been reported with sertraline if administered at the end of pregnancy and/or lactation (excitement, agitation, insomnia, sucking weakness).

4.7 Effects on ability to drive and use machines

Sertraline has minor or moderate influence on the 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 not 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 adverse reactions have been reported in clinical studies in which repeated doses were given:

Psychiatric disorders:
Very common: insomnia, somnolence, anorexia

Nervous system disorders:
Very common: tremor, dizziness

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

Renal and urinary disorders:
Very common: sexual disorders (mainly delayed ejaculation in men)

General disorders:
Common: increased sweating

Spontaneous reports of the following adverse events have been received in the post-marketing phase:

Blood and lymphatic system disorders:
Uncommon: purpura, altered platelet function, altered haemorrhagic diathesis (with e.g. epistaxis, gastrointestinal haemorrhage or haematuria)
Rare: leukopenia, thrombocytopenia

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

Metabolism and nutrition disorders:

Rare: hyponatraemia, which remitted on discontinuation of therapy. Isolated cases may have been attributable to syndrome of inappropriate ADH secretion. These adverse events have mainly occurred in elderly patients and in patients using diuretics or other medicinal products. Elevated serum cholesterol levels.

Psychiatric disorders:

Common: yawning, agitation, anxiety

Uncommon: euphoria, depressive symptoms, hallucinations, mania, hypomania

Rare: loss of libido (in women and men), nightmares, aggressive reactions, psychosis, suicidal thoughts / behaviour (see section 4.4)

Nervous system disorders:

Common: headache, motor disorders (including extrapyramidal symptoms, such as hyperkinesia, increased muscle tone, teeth-grinding and impaired gait), paraesthesiae, hypaesthesia

Uncommon: migraine

Rare: psychomotor restlessness / akathisia (see section 4.4), involuntary muscle contractions, coma, seizures, 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:

Common: impaired vision

Uncommon: mydriasis

Ear and labyrinth disorders:

Common: tinnitus

Cardiac disorders:

Common: chest pain, palpitations

Uncommon: hypertension, syncope, tachycardia

Vascular disorders:

Uncommon: peripheral oedema, periorbital oedema

Respiratory, thoracic and mediastinal disorders:

Rare: bronchospasm

Gastrointestinal disorders:

Common: obstipation, abdominal pain, vomiting

Uncommon: increased appetite, pancreatitis

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.

Skin and subcutaneous tissue disorders:

Common: skin rash

Uncommon: pruritus, alopecia, erythema multiforme

Rare: photosensitivity of skin, urticaria, Quincke's oedema, severe dermal exfoliation e.g. Stevens-Johnson syndrome and epidermal necrolysis

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 disorders

Rare: priapism

General disorders:

Common: asthenia, tiredness, hot flushes

Uncommon: indisposition, gain of body weight, loss of body weight, fever

Rare: anaphylactoid reaction, allergic reactions, allergy

Investigations:

Uncommon: 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 sertraline treatment 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 adverse events 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 adverse events 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

5.3 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, Selective serotonin reuptake inhibitors
ATC code: N06A B06

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 muscarinic, serotonergic, dopaminergic, histaminergic, benzodiazepine, GABA or adrenergic receptors. As in the case of other clinically effective antidepressants, there was down-regulation 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.

5.4 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 of once daily dosing; sertraline concentrations are doubled compared to plasma levels after initial dose with once daily administration.

Metabolism:

Sertraline and its 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 section 4.4.

5.3 Preclinical safety data

Conventional studies on sertraline did not demonstrate mutagenicity or carcinogenicity. No teratogenic effects have been observed in studies on reproduction toxicity in rats and rabbits. However, delay of ossification occurred in the fetuses of rats and rabbits in dosages exceeding the maximal therapeutic dose in humans 2.5- up to 10-fold. Administration of sertraline to rats during the last third of gestation and until the 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. The reduced post-natal survival was shown to be associated with *in utero* exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Cellulose, microcrystalline

Calcium hydrogen phosphate dihydrate
Povidone K-30
Croscarmellose sodium
Magnesium stearate
Coating - Opadry
Hypromellose
Titanium dioxide (E171)
Macrogol 6000
Polysorbate 80
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Transparent and white opaque PVC/PVdC aluminium blisters.
Pack sizes: 20, 28, 30, 50, 98, 100 and 200 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

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Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sertraline 50 and 100 mg Film-Coated Tablets
Sertraline hydrochloride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get 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**
2. **Before you take Sertraline Film-Coated Tablets**
3. **How to take Sertraline Film-Coated Tablets**
4. **Possible side effects**
5. **How to store Sertraline Film-Coated Tablets**
6. **Further information**

1. What Sertraline Film-Coated Tablets are and what they are used for

- Sertraline belongs to a group of drugs called selective serotonin re-uptake inhibitors (SSRIs). Serotonin is a chemical that, in the brain, passes messages between nerve cells and may help to control mood.
- Your medicine is used to treat depression.

2. Before you take Sertraline Film-Coated Tablets

Do not take Sertraline Film-Coated Tablets :
- If you are allergic (hypersensitive) to sertraline or any of the other ingredients of this medicine
- If you are taking monoamine oxidase inhibitors (MAOIs) e.g. moclobemide, selegiline or phenelzine (see 'Take special care with Sertraline Film-coated Tablets')
- If you are taking pimozide.

Take special care with Sertraline Film-Coated Tablets
Use in children and adolescents under 18 years old:
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 years and you want to discuss this, please go back to your doctor. You should inform your doctor if any

of the symptoms 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.

Speak to your doctor before taking this medicine:

- If you have recently completed treatment with medicines that belong to the group of MAO inhibitors, such as moclobemide (for depression) or selegiline (for Parkinson's disease): you must wait at least 14 days before you can start taking Sertraline Film-Coated Tablets unless your doctor has told you otherwise. Ask your doctor before you change from another antidepressant medicine to Sertraline Film-Coated Tablets. At least 2 weeks should elapse between discontinuation of Sertraline Film-Coated Tablets and initiation of therapy with any MAO inhibitor
- If you have liver problems: your doctor may need to adjust your dosage. You should not take Sertraline Film-Coated Tablets if you have severe liver problems
- If you have diabetes, as Sertraline Film-Coated Tablets may affect the control of your blood sugar levels so your medication may need adjusting
- If you have epilepsy, as sertraline rarely causes seizures (see "4. Possible side effects"). Should you experience seizures or an increase in seizure frequency whilst on sertraline, contact your doctor immediately, as you may need to stop taking Sertraline Film-Coated Tablets
- If you have a history of mania (periods of unusually elevated high mood and activity), as sertraline uncommonly causes manic reactions (see "4. Possible side effects"). Should you experience a manic reaction whilst on sertraline, contact your doctor immediately, as you may need to stop taking Sertraline Film-Coated Tablets
- If you have a history of schizophrenia, as sertraline may in rare cases worsen psychotic symptoms (see "4. Possible side effects")
- If you have a history of bleeding disorders or a tendency to bleed
- If you are taking medicines that cause an increased risk of bleeding, such as medicines to thin the blood (anticoagulants e.g. warfarin), neuroleptics (such as chlorpromazine or clozapine), tricyclic antidepressants (such as imipramine), painkillers (NSAIDs such as ibuprofen) or acetylsalicylic acid (e.g. aspirin) (see 'Taking other medicines')
- If you have heart disease or have recently had a heart attack
- If you are to receive electroconvulsive therapy (ECT).

You should be aware that you may not begin to feel better until you have been taking Sertraline Film-Coated Tablets for several weeks, and that you may experience an increase in thoughts of self harm or suicide and corresponding behaviour at the beginning of your treatment. If you or your carer notice such an increase, you must seek medical advice immediately.

Sertraline Film-Coated Tablets rarely cause problems with movement (such as feeling restless) or involuntary muscle contractions (see '4. Possible side effects'). These problems are more likely to occur in the first few weeks of treatment. You should tell your doctor if you experience these symptoms so the best decision can be made as to how to continue your treatment.

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 effect of Sertraline Film-Coated Tablets may be increased or decreased by other medicines and vice versa. These medicines include:

- MAO inhibitors such as moclobemide, phenelzine or selegiline (used to treat depression or Parkinson's disease): these medicines must not be used with Sertraline Film-Coated Tablets as

serious or even fatal reactions (serotonin syndrome) can occur (see 'Do not take Sertraline Film Coated Tablets' and 'Take special care with Sertraline Film-Coated Tablets')
- Pimozide (used to treat certain psychiatric conditions): this medicine must not be used with Sertraline Film-Coated Tablets (see 'Do not take Sertraline Film-Coated Tablets') because the combination could cause heart problems
- Tricyclic antidepressants, e.g. amitriptyline, clomipramine
- Tryptophan, fenfluramine or selective serotonin re-uptake inhibitors such as fluoxetine (other medicines for depression or migraine, for example): these medicines should not be used together with Sertraline Film-Coated Tablets as the combination could cause serotonin syndrome (a potentially life-threatening condition with high temperature, muscle stiffness or twitching, confusion, irritability and extreme agitation)
- Lithium (used to treat depression)
- Antipsychotics, e.g. chlorpromazine, haloperidol, olanzapine
- Tramadol or pethidine (painkillers), dextromethorphan (used to treat cough)
- Non-steroidal anti-inflammatory drugs (NSAIDs), e.g. acetylsalicylic acid (e.g. aspirin), diclofenac
- Sumatriptan (used to treat migraine)
- The herbal remedy St John's Wort (*Hypericum perforatum*)
- Diazepam (used to treat anxiety, sleeplessness, acute alcohol withdrawal, convulsions or muscle spasms)
- Medicines used to treat diabetes such as tolbutamide (see 'Take special care with Sertraline Film-Coated Tablets')
- Cimetidine (an anti-ulcer drug)
- Warfarin (an anti-coagulant drug)
- Diuretics (water tablets), e.g. spironolactone, triamterene
- Phenytoin (used to treat epilepsy).

Taking Sertraline Film-Coated Tablets with food and drink
Drinking alcohol is not recommended whilst being treated with Sertraline Film-Coated Tablets.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
The possible effects of Sertraline Film-Coated Tablets on the unborn child are unknown. You should, therefore, consult your doctor if you are pregnant or if you think you are pregnant.
The effects of Sertraline Film-Coated Tablets on the breast-feeding infant are unknown. You should, therefore, consult your doctor if you are breast-feeding.

Driving and using machines:
- Sertraline Film-Coated Tablets may affect your concentration or alertness. Do not drive or operate machinery until you are sure you are not affected.

3. How to take Sertraline Film-Coated Tablets

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.

The usual dosage instructions are given below:
Sertraline Film-Coated Tablets should be taken once a day.

The starting dose is one 50 mg tablet or half a 100 mg tablet (50 mg sertraline) taken daily. If necessary, your doctor may increase your dose, in steps of 50 mg at intervals of at least a week, up to two 50 mg tablets or one 100 mg tablet (100 mg sertraline) daily. The maximum daily dose is four 50 mg tablets or two 100 mg tablets (200 mg sertraline).

Children and adolescents:
Sertraline Film-Coated Tablets should not be used in children and adolescents under 18 years of age.
The elderly:
As low a dose as possible should be used.

Patients with liver problems:
The dose may be reduced or the interval between doses increased.

The tablets should be swallowed with a drink of water.
You should continue to take this medicine for as long as your doctor tells you to. This may be for some time (usually at least 6 months) after you start to feel better. This is to make sure that the symptoms do not come back. Do not stop taking your tablets suddenly as you may suffer from unwanted withdrawal symptoms. Your doctor will gradually reduce your dose.

If you take more Sertraline Film-Coated Tablets than you should
If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. An overdose can cause sleepiness, nausea, vomiting, a fast heart rate, shaking, agitation and dizziness. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take Sertraline Film-Coated Tablets
If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Take the remaining doses at the correct time.

If you stop taking Sertraline Film-Coated Tablets
Do not stop taking your tablets suddenly. When your doctor decides you should stop taking Sertraline Film-Coated Tablets, your dose will be reduced gradually over a period of time.
If you stop taking your tablets suddenly, you may experience the following effects:
- Shaking, dizziness, pins and needles, electric shock sensations
- Palpitations (sensations of irregular or forceful beating of the heart)
- Sweating, headache, visual disturbances
- Confusion, anxiety, agitation, feeling emotionally unstable, feeling irritable
- Sight problems
- Nausea and/or vomiting, diarrhoea
- Sleep disturbances including difficulty in sleeping and unusual dreams

These effects are usually mild, occur within the first few days after stopping taking Sertraline Film-Coated Tablets, and will gradually disappear.

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 you experience the following, stop taking Sertraline Film-Coated Tablets and tell your doctor immediately or go to the casualty department at your nearest hospital:

- A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat which may cause difficulty swallowing or breathing).

This is a very serious but rare side effect. You may need urgent medical attention or hospitalisation.

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 a condition known as serotonin syndrome. Although this syndrome only occurs rarely, it can be life-threatening. You may need to stop taking Sertraline Film-Coated Tablets.

If you are elderly, you may be more sensitive to the side effects of Sertraline Film-Coated Tablets.

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

Very common (affecting more than one person in 10):

- Difficulty sleeping, sleepiness
- Loss of appetite
- Shaking, dizziness
- Dry mouth
- Nausea, diarrhoea
- Impotence, problems with ejaculation.

Common (affecting fewer than one person in 10 but more than one person in 100):

- 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.
- Hyperactivity, changes in muscle tone, teeth-grinding, impaired gait (pattern of walking)
- Pins and needles, loss of feeling in the body
- Problems with sight, ringing in the ears
- Constipation, abdominal pain, vomiting
- Irregular periods
- Lethargy, tiredness.

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):

- Unusual bleeding (including nosebleeds and blood in the urine), unexplained bruising
- Abnormal feeling of well-being, feeling overexcited, manic reactions, depression, hallucinations
- Migraine, fainting
- 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 (affecting fewer than one person in 1,000 but more than one person in 10,000):
- 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)
- Problems with movement (such as feeling restless), involuntary muscle contractions
- Seizures
- Coma
- 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.

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 Film-Coated Tablets

Keep out of the reach and sight of children. Do not use Sertraline Film-Coated Tablets after the expiry date that is stated on the blister and outer packaging. The expiry date refers to the last date of the 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 (as hydrochloride).
Each 50 mg tablet contains 50 or 100 mg of sertraline.
Each 100 mg tablet contains 100 mg of sertraline.● The other ingredients are:
Core: microcrystalline cellulose, calcium hydrogen phosphate dihydrate, povidone K-30, croscarmellose sodium, magnesium stearate
Coating: Opadry, hypromellose, titanium dioxide (E171), macrogol 6000 and polysorbate 80. The 50 mg tablets also contain the colour indigo carmine
(E132)
The 100 mg tablets also contain the colours iron oxide yellow (E172) and iron oxide black (E172).

What Sertraline Film-Coated Tablets look like and contents of the pack:

● Sertraline 50 mg Film-Coated Tablets are light blue, film-coated elliptical shaped tablets, scored on one side and debossed "9" and "3" on
each side of the score, debossed with "7176" on the opposite side of the tablet● Sertraline 100 mg Film-Coated Tablets are light yellow, film-coated elliptical shaped tablets, scored on one side and debossed "9" and "3" on each side of the
score, debossed with "7177" on the opposite side of the tablet

- The 50 mg tablets are available in pack sizes* of 7, 10, 15, 20, 28, 30, 50, 60, 98, 100, 200, 294 or 300 tablets
- The 100 mg tablets are available in pack sizes* of 20, 28, 30, 50, 98, 100 or 200 tablets.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation holder and Company responsible for manufacture is: TEVA UK Limited, Eastbourne, BN22 9AG.

Distributed by TEVA UK, Leeds LS27 0JG.

This leaflet was last revised: November 2006

Module 4

Labelling

50 mg:

100 mg:

Each tablet contains 100 mg of sertraline
(as sertraline hydrochloride).
DOSAGE:
Please read the package leaflet before use.
KEEP OUT OF THE REACH
AND SIGHT OF CHILDREN.
Sertraline 100 mg Film-Coated Tablets
Please affix dispensary label here
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 0289/0561
83736-U
POM
® UK Reg'd T.M.
PIP 112-5152
5 017007 031321
Sertraline
100 mg Film-Coated Tablets
Sertraline
For Oral Use
100
mg
28
Tablets
TEVA
Sertraline 100 mg Film-Coated Tablets
28
Tablets
100
mg
47 x 16
x 134mm
1 2 3 4 5 6 7
8 9 10 11
12 13
14 15

Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Sertraline 50 mg Film-coated Tablets and Sertraline 100 mg Film-coated Tablets in the treatment of depressive illness, obsessive compulsive disorder and post-tramatic stress disorder could be approved. National marketing authorisations were granted on 12 December 2005.

EXECUTIVE SUMMARY

Problem statement

These are abridged Marketing Authorisation applications made using Mutual Recognition Procedure UK/H/861/01-02. National UK licenses (PL 00289/0560 and 00289/0561) were granted to TEVA UK Limited on 12 December 2005. The applicant claims essential similarity, under article 10.1 to Lustral Tablets, which were first authorised in the UK in 19 November 1990 (PL 00057/0308 and 00057/0309).

In support of the applications TEVA UK Limited has conducted a bioequivalence study using Lustral 100 mg tablets from the UK and Zoloft 50 mg capsules from France (both from Pfizer Limited) as the reference products.

About the product

Sertraline is a naphthaleneamine derivative and a selective serotonin re-uptake inhibitor, with actions and uses similar to those of fluoxetine. It is administered by mouth in the treatment of depression. The usual initial dose is 50 mg daily increased, if necessary, in increments of 50 mg at intervals of at least a week to a maximum of 200 mg daily.

The development programme

The objective of the development programme was to formulate a robust, stable, acceptable formulation of Sertraline 50 mg Film-coated Tablets and Sertraline 100 mg Film-coated Tablets, comparable in performance to Zoloft 50 mg capsules and Lustral 100 mg tablets, the reference products for these generic applications.

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

No new preclinical studies were conducted, which is acceptable given that the applications were based on essential similarity to products that have been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the applications were based on essential similarity to products 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 these products prior to granting the national authorisations.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

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.

PHARMACEUTICAL ASSESSMENT REPORT

ACTIVE SUBSTANCE

Sertraline is a chiral compound with two chiral centres at C1 and C4. It therefore exhibits two diastereioisomers, cis and trans. The active is the "cis (1S, 4S) isomer" or the "cis (+) isomer".

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

The certificates of analysis and results of in-house testing for typical batches are provided, demonstrating compliance with the proposed specification.

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

Appropriate stability data have been generated, supporting the retest period for the active substance.

DRUG PRODUCT

Sertraline 50mg Film-coated Tablets : Light blue, film-coated elliptical shaped tablet, on one side scored and debossed '9' and '3' from each side of the score. Debossed with '7176' on the opposite side of the tablet.
Sertraline 100mg Film-coated Tablets: Light yellow, film-coated elliptical shaped tablet, on one side scored and debossed '9' and '3' from each side of the score. Debossed with '7177' on the opposite side of the tablet.

Composition

The tablet cores contain sertraline hydrochloride, microcrystalline cellulose, calcium hydrogen phosphate dihydrate, povidone, croscarmellose sodium and magnesium stearate. The 50 mg tablets are coated in opadry 12F20984 blue (hypromellose (E464), titanium dioxide (E171), macrogol 6000, polysorbate 80 (E433) and indigo carmine (E132)) and the 100 mg tablets are coated in opadry 12F22609 yellow (hypromellose (E464), titanium dioxide (E171), macrogol 6000, polysorbate 80 (E433), iron oxide yellow (E172) and iron oxide black (E172)).

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:

- 20, 28, 30, 50, 98, 100 and 200 of the 100 mg tablets.
- 7, 10, 15, 20, 28, 30, 50, 60, 98, 100, 200, 294 and 300 of the 50 mg tablets.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, with no specific storage instructions.

Bioavailability/bioequivalence

A randomised, three-way, crossover, open-label, single dose study was carried out in healthy volunteers comparing TEVA UK Limited's Sertraline 100 mg Film-coated Tablets with Zoloft 2 x 50 mg capsules and Lustral 100 mg tablets. Certificates of Analysis are provided, demonstrating that the batches used in the study were tested and found to be satisfactory. The analytical report of the study is well presented and the test method and validation are satisfactory.

Results

Sertraline 100mg Film-coated Tablets vs. Lustral® 100mg tablets:

The mean relative bioavailability of sertraline was 113.72%, with a 90% confidence interval of 106.50 – 121.42% for the ratio of the In-transformed $AUC_{0\text{-inf}}$. The ratio of mean C_{max} In-transformed values was 117.55%, with a 90% confidence interval of 107.89 – 128.08%. The median T_{max} values were 7 and 6.5 hours for the test and reference products, respectively.

Sertraline 100mg Film-coated Tablets vs. Zoloft® 50mg capsules (2x):

The mean relative bioavailability of sertraline was 109.69%, with a 90% confidence interval of 102.73 – 117.13% for the ratio of the In-transformed $AUC_{0\text{-inf}}$. The ratio of mean C_{max} In-transformed values was 111.05%, with a 90% confidence interval of 101.93 – 120.99%. The median T_{max} value was 7 hours for both the test and reference products.

The difference between treatments for untransformed T_{max} was not statistically significant.

Results obtained are well within the 80 – 125% confidence interval for the AUC, slightly over the C_{maxx} but within the wider acceptance range of 71 – 133%. When compared to the capsules, the test tablets give results well within the 80 – 125% range for AUC and C_{max}.

In line with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the conclusions of the bioequivalence study conducted with the 100 mg tablets can be extrapolated to the 50 mg strength, the formula of which is homothetical to that used in the bioequivalence study and which have a similar dissolution profile.

It can be concluded that the test formulation containing 100 mg sertraline hydrochloride developed by TEVA UK Limited and the reference products have comparable bioavailability under fasting conditions.

CONCLUSIONS

A Marketing Authorisation may be granted for these products.

NON-CLINICAL ASSESSMENT REPORT

These applications for generic products claim essential similarity to Lustral Tablets (Pfizer Limited), which have been licensed 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 REPORT

INDICATIONS

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

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

Sertraline is also indicated for the treatment of paediatric patients with OCD.

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

DOSE & DOSE SCHEDULE

Sertraline should be given as a single daily dose. Sertraline Film-coated Tablets can be administered with or without food.

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

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

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

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

Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level. Dosage during prolonged maintenance therapy should be kept at the lowest effective level, with subsequent adjustments depending on therapeutic response. The onset of therapeutic effect may be seen within 7 days, although 2 - 4 weeks (and even

longer in OCD) are usually necessary for full activity. A longer treatment period, even beyond 12 weeks in some cases, may be required in the case of a therapeutic trial in PTSD.

Use in children aged 6 - 17 years: Treatment should only be initiated by specialists. The safety and efficacy of sertraline has been established in paediatric OCD patients (aged 6 - 17). The administration of sertraline to paediatric OCD patients (aged 13 - 17) should commence at 50 mg/day. Therapy for paediatric OCD patients (aged 6 - 12) should commence at 25 mg/day, increasing to 50 mg/day after 1 week. Subsequent doses may be increased in case of lack of response in 50 mg/day increments up to 200 mg/day as needed. However, the generally lower body weights of children compared to adults should be taken into consideration in advancing the dose from 50 mg, in order to avoid excessive dosing. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week.

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

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

Sertraline tablets are for oral administration only.

TOXICOLOGY

No new data submitted.

CLINICAL PHARMACOLOGY

The applicant has submitted a single dose comparative bioavailability study. Mean relative bioavailability of test product and reference was 113.72%, with a 90% CI of 106.50 - 121.42% for the ratio of log transformed $AUC_{0\text{-inf}}$. The ratio of mean C_{max} was 117.55%, with 90% CI 107.89 - 128.08%.

EFFICACY

No new data presented.

SAFETY

No new data presented.

EXPERT REPORTS

A clinical summary by an appropriately qualified person has been submitted

PATIENT INFORMATION LEAFLET (PIL)

The PIL is satisfactory

LABELLING

All labelling is satisfactory

APPLICATION FORM (MAA)

The form submitted in support of this MA application is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory and fully consistent with that of the cross-reference product

DISCUSSION

The applicant has satisfactorily demonstrated comparative bioequivalence and, hence, essential similarity to the reference brand leader product.

MEDICAL CONCLUSION

Marketing authorisation is recommended

OVERALL CONCLUSION

QUALITY

The important quality characteristics of Sertraline 50 mg Film-coated Tablets and Sertraline 100 mg Film-coated 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 tablets and Zoloft capsules and Lustral tablets.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the products 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 is considered to have demonstrated the therapeutic value of the compound. The risk benefit balance is therefore considered to be positive.

Module 6

Steps take after initial procedure

No further steps have yet been taken following initial procedure.