

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sertral 50 mg film-coated tablet
Sertral 100 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

50 mg tablets:

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

100 mg tablets:

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

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

50 mg tablets:

White to off-white, capsule-shaped, film-coated tablets, scored on one side and printed with "50" on the other. Size 4.2x10.3 mm.

100 mg tablets:

White to off-white, capsule-shaped, film-coated tablets, scored on one side and printed with "100" on the other. Size 5.2x13.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

Treatment of obsessive-compulsive disorder (OCD).

Treatment of obsessive compulsive disorder (OCD) in adolescents (13-17 years of age) (See section 4.2).

4.2 Posology and method of administration

Major depressive episodes in adults

The usual daily dose is 50mg sertraline.

If required, the dose can be increased to 100mg sertraline/day.

The maximum daily dose is 200mg sertraline.

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

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

Obsessive-compulsive disorder (OCD)

Adults

Initially 50 mg once daily. If dose increments are required, these should be made in steps of 50 mg at minimum intervals of 1 week. Dose changes should not be performed more than once per week due to the elimination half-life of sertraline being 24 hours. The maximum daily dose is 200 mg.

Adolescents (13-17 years of age)

Initiation of treatment and follow-up should be carried out by a specialist in child or adolescent psychiatry.

Initially 50 mg as a single daily dose. If dose increments are required, these should be made in steps of 50 mg at minimum intervals of some weeks. The maximum dose in adolescents under 18 years of age is 200 mg daily. Lower doses should however be considered in patients with low body weight to avoid elevated plasma levels.

Children and adolescents (under 18 years of age)

Sertral should not be used in the treatment of children and adolescents under the age of 18 years, except for adolescents (13-17 years of age) with obsessive-compulsive disorder (OCD) (see section 4.4).

Elderly

As the elimination half-life may be prolonged in elderly patients, it is recommended that the dosage is 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 (see section 4.4).

Method and duration of administration:

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

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

Patients should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

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 MAOIs (monoamine oxidase inhibitors) including selegiline, moclobemide and linezolid (see section 4.4).

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

4.4 Special warnings and special precautions for use

Serotonin syndrome

On rare occasions development of a serotonin syndrome (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) may occur in association with sertraline treatment, particularly when the drug is given in combination with MAOIs or other serotonergic medicinal products.

As this syndrome may result in potentially life-threatening conditions, treatment with sertraline should be discontinued if such events occur and supportive symptomatic treatment should be initiated.

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

Treatment with sertraline can be initiated at the earliest two weeks after discontinuation of an irreversible MAOI (e.g. selegiline), or at least 24 hrs after discontinuation of a reversible MAOI with a short half-life (e.g. moclobemide). At least 2 days should elapse between discontinuation of linezolid and initiation of treatment with sertraline. At least two weeks should elapse between discontinuation of sertraline and initiation of therapy with any MAOI. The dosage of sertraline should be increased gradually until an optimal response is attained.

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

Changeover from use of SSRIs or other antidepressants

A changeover from use of other selective serotonin reuptake inhibitors or other antidepressants should be done cautiously in order to avoid possible pharmacodynamic

interactions.

Careful clinical monitoring is especially important when sertraline is initiated after discontinuation of an antidepressant with a long half-life such as e.g. fluoxetine. There is no well documented evidence of the duration of treatment free interval required when switching from one antidepressant to another. See also section 4.5.

Children and adolescents (< 18 years):

Sertraline should not be used in the treatment of children and adolescents under the age of 18 years, except in the case of adolescents (13-17 years) with obsessive-compulsive disorder (OCD). In clinical trials, suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed among children and adolescents treated with antidepressants than 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 regarding growth, maturation, cognitive and behavioural development are lacking.

Suicide/suicidal ideation

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

Other psychiatric conditions for which sertraline is prescribed can also be associated with an increased risk of suicide-related events. These conditions may co-exist 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, or 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.

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

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 clinical studies, approximately 0.4 % of patients treated with sertraline developed mania or hypomania. 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 developing a manic phase.

Schizophrenia:

Psychotic symptoms might become aggravated in schizophrenic patients.

Withdrawal symptoms seen on discontinuation

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

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

Washout period of SSRI

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

Haemorrhage:

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Caution is advised in patients taking SSRIs, particularly when these are used concomitantly 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 medicinal products (NSAIDs)) as well as in patients with a history of bleeding disorders (also see section 4.5).

Electroconvulsive therapy (ECT):

Caution is advisable, since there is little clinical experience of concurrent administration of sertraline with ECT.

Diabetes:

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

Cardiac disease:

The safety of sertraline has not been established in patients who have recently suffered a heart attack or patients with 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 (Electrocardiogram) abnormalities.

Elderly:

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

Impaired hepatic function:

Sertraline is extensively metabolised in the liver. A pharmacokinetic study of repeated doses in patients with mild and stabilised cirrhosis revealed a prolonged elimination half-life and an approximately threefold increase in 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 (See also 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. Following repeated dosing, in patients with mild to moderate (creatinine clearance 30 to 60ml/min) or moderate to severe (creatinine clearance 10 to 29ml/min) renal impairment the pharmacokinetic parameters (AUC_{0-24} and C_{\max}), 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 with the drug's low renal elimination rate, the dosage of sertraline does not have to be adjusted in case of impaired renal function.

Convulsive disorders

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

Lactose intolerance

Sertral contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions 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 inhibitors moclobemide and linezolid, see sections 4.3 and 4.4.

Pimozide:

Increased pimozide plasma levels have been observed in a clinical study after concomitant administration of sertraline and a low single dose of pimozide (2 mg). These increased levels have not been associated with ECG-changes. The mechanism of this interaction is unknown. The concomitant administration of sertraline and pimozide is contraindicated, because co-administration 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:

Serotonergic substances, such as other SSRIs, tryptophan, fenfluramine, dextromethorphan, pethidine, tramadol and serotonin agonists, should not be used concurrently with sertraline (see section 4.4).

Hypericum perforatum:

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

Precautions:

Other medicinal products:

Medicinal products bound to plasma proteins:

Due to the high protein binding of sertraline, interactions with other substances which are also 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 with diazepam or tolbutamide resulted in slight, but statistically significant changes to various pharmacokinetic parameters. Cimetidine reduced the rate of elimination of concurrently administered sertraline. The clinical relevance of these effects is unclear.

Sertraline had no influence on the efficacy of atenolol; there were no interactions with glibenclamide or digoxin.

Lithium:

There were no changes in the pharmacokinetics of lithium, on concomitant administration of lithium and sertraline in placebo-controlled studies in healthy subjects. There was, however, an increased incidence of tremor in comparison with patients receiving placebo, indicating that there may be a pharmacodynamic interaction. Patients receiving lithium and sertraline or other substances exerting a serotonergic effect should be appropriately monitored.

Sumatriptan:

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

CNS active medicinal products and alcohol:

In healthy patients, concomitant administration of sertraline 200 mg daily did not increase the psychomotor and cognitive function effects of alcohol, carbamazepine, haloperidol or phenytoin. Consumption of alcohol in conjunction with sertraline treatment is however, not recommended.

Hypoglycaemic substances:

Sertraline may alter glycaemic control. Therefore it is advisable to monitor the blood glucose level when initiating sertraline in diabetic patients.

See section 4.4.

Oral anticoagulants, salicylic acid derivatives 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 “Medicinal products bound to plasma proteins” and “Cytochrome P450 interactions / 2C9).

There is a potentially increased risk of bleeding when SSRIs are combined with other oral anticoagulants, salicylic acid derivatives NSAID, atypical antipsychotics, phenothiazines, and most tricyclic antidepressants (see section 4.4).

Diuretics

Diuretics used concomitantly with sertraline may predispose elderly patients to hyponatraemia and SIADH (Syndrome of Inappropriate Anti-Diuretic Hormone secretion).

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 50mg/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 200mg 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 the plasma concentrations of tolbutamide, phenytoin and warfarin shows that sertraline does not inhibit CYP 2C9 to any 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 indicates 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 inhibiting of CYP 1A2.

Phenytoin:

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

Changeover from use of SSRIs or other antidepressants:

See section 4.4.

Phenazone (Antipyrine):

The half-life of antipyrine is reduced by concomitant administration of sertraline. This indicates a clinically non-significant hepatic enzyme induction.

4.6 Pregnancy and lactation

Pregnancy

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

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

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

Lactation

Sertraline is known to be excreted in breast milk (milk/plasma-ratio approx. 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 the potential risks to the child.

4.7 Effects on ability to drive and use machines

Clinical pharmacology studies have shown that sertraline has no or negligible influence on the psychomotor behaviour. Following treatment with psychotropic agents, however, the reaction time can be impaired in some patients. Patients are therefore advised to be careful when engaging with activities that require attention, such as driving or using dangerous machines, particularly till they get to know how sertraline treatment affects them.

4.8 Undesirable effects

The following undesirable effects have been reported in clinical studies and in the post-marketing phase:

Assessment of frequencies:

Very common: > 1/10 of patients treated
Common: > 1/100, < 1/10 of patients treated
Uncommon: > 1/1,000, < 1/100 of patients treated
Rare: > 1/10,000, < 1/1,000 of patients treated
Very rare: < 1/10,000 of patients treated including isolated reports

Blood and lymphatic system disorders

Uncommon: purpura, altered platelet function, haemorrhagic diathesis typically including: epistaxis, gastrointestinal haemorrhage or haematuria

Rare: leukopenia, thrombocytopenia

Endocrine disorders

Rare: gynaecomastia, hyperprolactinaemia, galactorrhoea, hypothyroidism, syndrome of inappropriate ADH secretion (SIADH).

Metabolism and nutrition disorders

Rare: hyponatraemia, elevated serum cholesterol levels.

Hyponatraemia generally reverses on discontinuation of therapy. Some cases possibly arise due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of reports were associated with older patients, and patients taking diuretics or otherwise volume depleted.

Psychiatric disorders

Very common: insomnia, somnolence, anorexia

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

Very common: tremor, dizziness, dry mouth

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

Uncommon: migraine

Rare: involuntary muscle contractions, coma, seizures, akathisia/psychomotor restlessness (see section 4.4), signs and symptoms associated with serotonin syndrome: agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia. In some cases, these symptoms occurred in association with the concomitant use of serotonergic agents.

Eye disorders

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, peri-orbital oedema

Respiratory, thoracic and mediastinal disorders

Rare: bronchospasm

Gastrointestinal disorders

Very common: nausea, diarrhoea/loose stool
Common: dyspepsia, constipation, 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 in transaminase levels mainly occur in the initial 9 weeks of treatment and rapidly disappear after discontinuation of therapy.

Skin and subcutaneous tissue disorders

Common: skin rash
Uncommon: pruritus, alopecia, erythema multiforme
Rare: photosensitivity, urticaria, Quincke's oedema, severe dermal exfoliation e.g. Stevens-Johnson syndrome and epidermal necrolysis

Musculoskeletal and connective tissue disorders

Uncommon: arthralgia

Renal and urinary tract disorders

Uncommon: urinary incontinence
Rare: urinary retention

Reproductive system and breast disorders

Very common: sexual disorders (mainly delayed ejaculation in men)
Common: menstrual disorders
Rare: priapism

General disorders and administration site conditions

Common: asthenia, tiredness, hot flushes
Uncommon: malaise, gain of body weight, loss of body weight, fever
Rare: facial oedema, anaphylactoid reactions, allergic reactions, allergy

Investigations:

Uncommon: abnormal laboratory values

In clinical trials, male sexual dysfunction has been reported in 23% of the male patients (corrected for placebo) treated for social phobias. The adverse reactions are dose dependent and often transient when the treatment is continued.

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 population. The types and frequency of undesirable effects in the elderly patients were similar to those in younger patients.

4.9 Overdose

Symptoms of overdose

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

Toxicity

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

Treatment

There is no known specific antidote to sertraline overdose. The following measures are recommended: ensure airways are free and that adequate ventilation and oxygen 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 recommended 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 re-uptake inhibitor.
ATC code: N06AB06.

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

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

As a result of its selective inhibition of serotonin reuptake, sertraline does not influence catecholamine activity. In addition, sertraline has no affinity for muscarinergic, serotonergic, dopaminergic, histaminergic, benzodiazepine, GABA or adrenergic receptors. Long term use of sertraline is associated with downregulation of cerebral norepinephrine receptors.

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 attained after 4.5 – 8.4 hours.

On the basis of recovery rates in urine and faeces, it can be estimated that absorption after oral administration is at least 70 %. Bioavailability is reduced by the first pass effect.

Concomitant consumption of food does not significantly influence the bioavailability of sertraline tablets.

Distribution:

Plasma protein binding of sertraline is approximately 98 %. Data from animal studies indicate that sertraline has a large volume of distribution.

Steady-state concentrations are thus reached after approximately 1 week and sertraline concentrations are doubled compared to plasma levels after initial dose with once daily administration.

Metabolism:

Both sertraline and the main metabolite, N-desmethylsertraline undergo extensive hepatic metabolism. *In vitro* N-desmethylsertraline exhibits considerably less (by a factor of approx. 20) activity than the parent substance. The metabolite exerts no effect on *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 impaired hepatic function, see sections 4.2 and 4.4.

5.3 Preclinical safety data

Conventional studies on sertraline did not demonstrate mutagenicity or carcinogenicity. No teratogenic effects were observed in rats and rabbits. However, delayed ossification occurred in rat and rabbit foetuses at doses 2.5-fold to 10-fold the maximum therapeutic dose in humans. Administration of sertraline to rats during the last trimester of gestation and until the end of lactation at doses 5-fold the maximum therapeutic dose in humans resulted in an increased number of stillbirths and a reduction in survival and body weight of the offspring. The reduced post-natal survival was shown to be associated with *in utero* rather than post-natal exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Silica, colloidal anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Copovidone
Lactose monohydrate
Magnesium stearate

Film coating:

Hypromellose
Hydroxypropylcellulose
Macrogol
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

50 mg and 100 mg: Blisters PVC/Al, 14, 20, 28, 30, 42, 50, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling, and disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Ltd.

B16, Bulebel Industrial Estate
Zejtun ZTN 08
Malta

8 MARKETING AUTHORISATION NUMBER

50 mg: MA245/00401
100 mg: MA245/00402

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12th December 2005

10 DATE OF REVISION OF THE TEXT

20th April 2007