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Module 1.3.1	Summary of Product Characteristics	Replaces: 2018-09-06

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sertraline Apotex 50 mg, filmomhulde tabletten
Sertraline Apotex 100 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sertraline Apotex 50 mg film-coated tablets: Each film-coated tablet contains sertraline hydrochloride equivalent to 50 mg sertraline.
Sertraline Apotex 100 mg film-coated tablets: Each film-coated tablet contains sertraline hydrochloride equivalent to 100 mg sertraline.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Sertraline 50mg film-coated tablets are 4 x 8 mm bluish purple oval scored film coated tablets engraved "APO" on one side, "SE" bisect "50" on the other side.

Sertraline 100mg film-coated tablets are 5 x 10 mm yellow oval scored film coated tablets engraved "APO" on one side, "SER" bisect "100" on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sertraline is indicated for the treatment of:
Major depressive episodes. Prevention of recurrence of major depressive episodes.
Panic disorder, with or without agoraphobia.
Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years.
Social anxiety disorder.
Post traumatic stress disorder (PTSD).

4.2 Posology and method of administration

Posology

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Initial treatment

Depression and OCD

Sertraline treatment should be started at a dose of 50 mg/day.

Panic Disorder, PTSD, and Social Anxiety Disorder

Therapy should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.

Titration

Depression OCD, Panic Disorder, Social Anxiety Disorder and PTSD:

Patients not responding to a 50 mg dose may benefit from dose increases. Dose changes should be made in steps of 50 mg at intervals of at least one week, up to a maximum of 200 mg/day. Changes in dose should not be made more frequently than once per week given the 24-hour elimination half life of sertraline.

The onset of therapeutic effect may be seen within 7 days. However, longer periods are usually necessary to demonstrate therapeutic response, especially in OCD.

Maintenance

Dosage during long-term therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response.

Depression

Longer-term treatment may also be appropriate for prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during current episode. Patients with depression should be treated for a sufficient period of time of at least 6 months to ensure they are free from symptoms.

Panic disorder and OCD

Continued treatment in panic disorder and OCD should be evaluated regularly, as relapse prevention has not been shown for these disorders.

Use in the elderly

Elderly should be dosed carefully, as elderly may be more at risk for hyponatraemia (see section 4.4).

Use in hepatic insufficiency

The use of sertraline in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment (see section 4.4). Sertraline should not be used in cases of severe hepatic impairment as no clinical data are available (see section 4.4).

Use in renal insufficiency

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No dosage adjustment is necessary in patients with renal insufficiency (see section 4.4).

Paediatric Patients

Children and adolescents with obsessive compulsive disorder

Age 13-17 years: Initially 50 mg once daily.

Age 6-12 years: Initially 25 mg once daily. The dosage may be increased to 50 mg once daily after one week.

Subsequent doses may be increased in case of less than desired response in 50 mg increments over a period of some weeks, as needed. The maximum dosage is 200 mg daily. However, the generally lower body weights of children compared to those of adults should be taken into consideration when increasing the dose from 50 mg. Dose changes should not occur at intervals of less than one week.

Efficacy is not shown in paediatric major depressive disorder.

No data is available for children under 6 years of age (see also section 4.4)

Method of administration

Sertraline should be administered once daily, either in the morning or evening.

Sertraline tablets can be administered with or without food.

Withdrawal symptoms seen on discontinuation of sertraline

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 sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see section 4.5).

Concomitant intake of pimozide is contraindicated (see section 4.5).

4.4. Special warnings and precautions for use

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)

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The development of potentially life-threatening syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) has been reported with SSRIs, including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of other serotonergic drugs (including other serotonergic antidepressants, triptans), with drugs which impair metabolism of serotonin (including MAOIs e.g. methylene blue), antipsychotics and other dopamine antagonists, and with opiate drugs. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome (see section 4.3 – Contraindications).

Switching from Selective Serotonin Reuptake Inhibitors (SSRIs), antidepressants or antiobsessional drugs

There is limited controlled experience regarding the optimal timing of switching from SSRIs, antidepressants or antiobsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents such as fluoxetine.

Other serotonergic drugs e.g. tryptophan, fenfluramine and 5-HT agonists

Co-administration of sertraline with other drugs which enhance the effects of serotonergic neurotransmission such as amphetamines, tryptophan or fenfluramine or 5-HT agonists, or the herbal medicine, St John's Wort (*hypericum perforatum*), should be undertaken with caution and avoided whenever possible due to the potential for a pharmacodynamic interaction.

QTc extension / Torsade de Pointes (TdP)

Cases of QTc prolongation and TdP have been reported during postmarketing use of sertraline. The majority of cases occurred in patients with other risk factors for QTc extension/ TdP. The effect on QTc prolongation was confirmed in a thorough QTc study at healthy volunteers with a statistically significant positive exposure / response relationship. Therefore sertraline should be used with caution in patients with additional risk factors for QTc prolongation such as heart disease, hypokalemia or hypomagnesaemia, family history of QTc prolongation, bradycardia and concomitant use of drugs containing the QTc interval renew (see sections 4.5 and 5.1).

Activation of hypomania or mania

Manic/hypomanic symptoms have been reported to emerge in a small proportion of patients treated with marketed antidepressant and antiobsessional drugs, including sertraline. Therefore sertraline should be used with caution in patients with a history of mania/hypomania. Close surveillance by the physician is required. Sertraline should be discontinued in any patient entering a manic phase.

Schizophrenia

Psychotic symptoms might become aggravated in schizophrenic patients.

Seizures

Seizures may occur with sertraline therapy: sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

Suicide/suicidal thoughts/suicide attempts or clinical worsening

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

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

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Paediatric Patients

Sertraline should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with obsessive compulsive disorder aged 6-17 years old. 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 appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, sexual maturation and cognitive and behavioural development are limited. A few cases of retarded growth and delayed puberty post-marketing have been reported. The clinical relevance and causality are still unclear (see section 5.3 for the preclinical concerned safety data). Physicians must monitor paediatric patients on long term treatment for abnormalities in these body systems.

Abnormal bleeding/Haemorrhage

There have been reports of bleeding abnormalities with SSRIs including cutaneous bleeding (ecchymoses and purpura) and other haemorrhagic events such as gastrointestinal or gynaecological bleeding, including fatal haemorrhages. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g.

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anticoagulants, 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 (see section 4.5).

Hyponatraemia

Hyponatraemia may occur as a result of treatment with SSRIs or SNRIs including sertraline. In many cases, hyponatraemia appears to be the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium levels lower than 110 mmol/l have been reported.

Elderly patients may be at greater risk of developing hyponatraemia with SSRIs and SNRIs. Also patients taking diuretics or who are otherwise volume-depleted may be at greater risk (see Use in elderly). Discontinuation of sertraline should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatraemia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Withdrawal symptoms seen on discontinuation of sertraline treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, among patients treated with sertraline, the incidence of reported withdrawal reactions was 23% in those discontinuing sertraline compared to 12% in those who continued to receive sertraline treatment.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur 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).

Akathisia/psychomotor restlessness

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

Hepatic impairment

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Sertraline is extensively metabolised by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half life and approximately threefold greater AUC and C_{max} in comparison to normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of sertraline in patients with hepatic disease must be approached with caution. If sertraline is administered to patients with hepatic impairment, a lower or less frequent dose should be considered. Sertraline should not be used in patients with severe hepatic impairment (see section 4.2).

Renal impairment

Sertraline is extensively metabolised, and excretion of unchanged drug in urine is a minor route of elimination. In studies of patients with mild to moderate renal impairment (creatinine clearance 30-60 ml/min) or moderate to severe renal impairment (creatinine clearance 10-29 ml/min), multiple-dose pharmacokinetic parameters (AUC₀₋₂₄ or C_{max}) were not significantly different compared with controls. Sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Use in elderly

Over 700 elderly patients (>65 years) have participated in clinical studies. The pattern and incidence of adverse reactions in the elderly was similar to that in younger patients.

SSRIs or SNRIs including sertraline have however been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse event (see Hyponatraemia in section 4.4).

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or concomitant oral hypoglycaemic medicinal products may need to be adjusted.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Electroconvulsive therapy

There are no clinical studies establishing the risks or benefits of the combined use of ECT and sertraline.

Grapefruit juice

The administration of sertraline with grapefruit juice is not recommended (see section 4.5).

Interference with urine screening tests

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking sertraline. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of sertraline therapy.

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Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines.

Angle-Closure Glaucoma

SSRIs including sertraline may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. Sertraline should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

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

Contraindicated

Monoamine oxidase inhibitors:

Irreversible (non-selective) MAOIs (selegiline)

Sertraline must not be used in combination with irreversible (non-selective) MAOIs such as selegiline. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible (non-selective) MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible (non-selective) MAOI (see section 4.3).

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of sertraline with a reversible and selective MAOI, such as moclobemide, is not recommended. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of sertraline treatment. It is recommended that sertraline should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.3).

Reversible, non-selective MAOI (linezolid)

The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with sertraline (see section 4.3).

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI (e.g. methylene blue) and started on sertraline, or have recently had sertraline therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

Pimozide

Increased pimozide levels of approximately 35% have been demonstrated in a study of a single low dose pimozide (2 mg). These increased levels were not associated with any changes in EKG. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated (see section 4.3).

Co-administration with sertraline is not recommended

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CNS depressants and alcohol

The co-administration of sertraline 200 mg daily did not potentiate the effects of alcohol, carbamazepine, haloperidol, or phenytoin on cognitive and psychomotor performance in healthy subjects; however, the concomitant use of sertraline and alcohol is not recommended.

Other serotonergic drugs

See section 4.4.

Caution is also advised with fentanyl (used in general anaesthesia or in the treatment of chronic pain), other serotonergic drugs (including other serotonergic antidepressants, triptans), and with other opiate drugs.

Special Precautions

Medicines that prolong the QT interval

The risk of QTc prolongation and / or ventricular arrhythmias (eg TdP) may be increased when concomitant use of other medicines that prolong the QTc interval (e.g. certain conditions) antipsychotics and antibiotics) (see sections 4.4 and 5.1).

Lithium

In a placebo-controlled trial in normal volunteers, the co-administration of sertraline with lithium did not significantly alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When co-administering sertraline with lithium, patients should be appropriately monitored.

Phenytoin

A placebo-controlled trial in normal volunteers suggests that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, as some case reports have emerged of high phenytoin exposure in patients using sertraline, it is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels. It cannot be excluded that other CYP3A4 inducers, e.g. phenobarbital, carbamazepine, St John's Wort, rifampicin may cause a reduction of sertraline plasma levels.

Triptans

There have been rare post-marketing reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. Symptoms of serotonergic syndrome may also occur with other products of the same class (triptans). If concomitant treatment with sertraline and triptans is clinically warranted, appropriate observation of the patient is advised (see section 4.4).

Warfarin

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Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time, which may in some rare cases unbalance the INR value.

Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Other drug interactions, digoxin, atenolol, cimetidine

Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction of sertraline 200 mg daily was observed with digoxin.

Drugs affecting platelet function

The risk of bleeding may be increased when medicines acting on platelet function (e.g. NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might increase bleeding risk are concomitantly administered with SSRIs, including sertraline (see section 4.4).

Neuromuscular blockers

SSRIs can reduce the choline esterase activity in the plasma, resulting in an prolongation of action of the neuromuscular blocker mivacurium or other neuromuscular blockers.

Drugs Metabolized by Cytochrome P450

Sertraline may act as a mild-moderate inhibitor of CYP 2D6. Chronic dosing with sertraline 50 mg daily showed moderate elevation (mean 23%-37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isozyme activity). Clinical relevant interactions may occur with other CYP 2D6 substrates with a narrow therapeutic index like class 1C antiarrhythmics such as propafenone and flecainide, TCAs and typical antipsychotics, especially at higher sertraline dose levels.

Sertraline does not act as an inhibitor of CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2 to a clinically significant degree. This has been confirmed by *in-vivo* interaction studies with CYP3A4 substrates (endogenous cortisol, carbamazepine, terfenadine, alprazolam), CYP2C19 substrate diazepam, and CYP2C9 substrates tolbutamide, glibenclamide and phenytoin. *In vitro* studies indicate that sertraline has little or no potential to inhibit CYP 1A2.

Intake of three glasses of grapefruit juice daily increased the sertraline plasma levels by approximately 100% in a cross-over study in eight Japanese healthy subjects. Therefore, the intake of grapefruit juice should be avoided during treatment with sertraline (see section 4.4).

Based on the interaction study with grapefruit juice, it cannot be excluded that the concomitant administration of sertraline and potent CYP3A4 inhibitors, e.g. protease inhibitors, ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin and nefazodone, would result in even larger increases in exposure of sertraline. This also concerns moderate CYP3A4 inhibitors, e.g. aprepitant, erythromycin, fluconazole, verapamil and diltiazem. The intake of potent CYP3A4 inhibitors should be avoided during treatment with sertraline.

Sertraline plasma levels are enhanced by about 50% in poor metabolizers of CYP2C19 compared to rapid metabolizers (see section 5.2). Interaction with strong inhibitors of CYP2C19, e.g.

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omeprazole, lansoprazole, pantoprazole, rabeprazole, fluoxetine, fluvoxamine cannot be excluded.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no well controlled studies in pregnant women. However, a substantial amount of data did not reveal evidence of induction of congenital malformations by sertraline. Animal studies showed evidence for effects on reproduction probably due to maternal toxicity caused by the pharmacodynamic action of the compound and/or direct pharmacodynamic action of the compound on the foetus (see 5.3).

Use of sertraline during pregnancy has been reported to cause symptoms, compatible with withdrawal reactions, in some neonates, whose mothers had been on sertraline. This phenomenon has also been observed with other SSRI antidepressants. Sertraline is not recommended in pregnancy, unless the clinical condition of the woman is such that the benefit of the treatment is expected to outweigh the potential risk.

Neonates should be observed if maternal use of sertraline continues into the later stages of pregnancy, particularly the third trimester. The following symptoms may occur in the neonate after maternal sertraline 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 in sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Lactation

Published data concerning sertraline levels in breast milk show that small quantities of sertraline and its metabolite N-desmethylsertraline are excreted in milk. Generally negligible to undetectable levels were found in infant serum, with one exception of an infant with serum levels about 50% of the maternal level (but without a noticeable health effect in this infant). To date, no adverse effects on the health of infants nursed by mothers using sertraline have been reported, but a risk cannot be excluded. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefit outweighs the risk.

Fertility

Animal data did not show an effect of sertraline on fertility parameters (see section 5.3.). Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

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4.7. Effects on ability to drive and use machines

Clinical pharmacology studies have shown that Sertraline has no effect on psychomotor performance. However, as psychotropic drugs may impair the mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly.

4.8. Undesirable effects

Nausea is the most common undesirable effect. In the treatment of social anxiety disorder, sexual dysfunction (ejaculation failure) in men occurred in 14% for sertraline vs 0% in placebo. These undesirable effects are dose dependent and are often transient in nature with continued treatment. The undesirable effects profile commonly observed in double-blind, placebo-controlled studies in patients with OCD, panic disorder, PTSD and social anxiety disorder was similar to that observed in clinical trials in patients with depression.

Table 1 displays adverse reactions observed from postmarketing experience (frequency not known) and placebo-controlled clinical trials (comprising a total of 2542 patients on sertraline and 2145 on placebo) in depression, OCD, panic disorder, PTSD and social anxiety disorder.

Some adverse drug reactions listed in Table 1 may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Table 1: Adverse Reactions

Frequency of adverse reactions observed from placebo-controlled clinical trials in depression, OCD, panic disorder, PTSD and social anxiety disorder. Pooled analysis and postmarketing experience (frequency not known).

Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)		Frequency not Known
<i>Infections and Infestations</i>					
	upper respiratory tract infection, pharyngitis rhinitis	gastroenteritis, otitis media	diverticulitis [§] ,		
<i>Neoplasms benign, malignant (including cysts and polyps)</i>					
		Neoplasm			

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<i>Blood and lymphatic system disorders</i>					
			leukopenia, *§, thrombocytopenia*§, lymphadenopathy*,		
<i>Immune system disorders</i>					
		hypersensitive*, seasonal allergy*,	anaphylactoid reaction*		,
<i>Endocrine disorders</i>					
		hypothyroidism*	hyperprolactinemia * §, inappropriate secretion of the antidiuretic hormone *§		
<i>Metabolism and Nutrition Disorders</i>					
	reduced appetite, increased appetite*		hypercholesterolemia , diabetes mellitus *, hypoglycemia *, hyperglycemia *§, hyponatremia * §		
<i>Psychiatric Disorders</i>					
Insomnia (19%)	depression*, de- personalisation, nightmare, anxiety*, agitation*, nervousness, reduced libido*, bruxism	hallucination*, euphoric mood*, apathy, abnormal thoughts, suicidal ideation/ suicidal behavior, psychotic disorder*, aggressiveness*, Paranoia	conversion disorder*§, drug dependence, , sleep walking, premature ejaculation, paroniria*§		
<i>Nervous System Disorders</i>					
dizziness, somnia	paraesthesias*, tremor,	amnesia,	coma*, akathisia (see section 4.4),		

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E, headache*	hypertonia*, concentration disorder and dysgeusia, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, dystonia, teeth grinding or staggering gait),	hypo- aesthesia*, involuntary muscle contractions*, syncope*, hyperkinesia* , migraine*, convulsions*, dizziness which is dependent on posture, abnormal co- ordination, speech disorder	dyskinesia, hyperaesthesia, cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call- Fleming syndrome)*§, psychomotor restlessness*§ (see section 4.4), sensory disturbance and choreoathetosis§ are also reported signs and symptoms associated with serotonin syndrome* or malignant neuroleptic syndrome (in some cases associated with the concomitant use of serotonergic medicines), including agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, stiffness and tachycardia§		
<i>Eye Disorders</i>					
	visual disturbance*	Mydriasis*	scotoma, glaucoma, diplopia, photophobia, hemophthalmia*§, uneven pupils*§, abnormal vision§, abnormality of tear		Maculopathy
<i>Ear and Labyrinth Disorders</i>					
	Tinnitus*	ear pain			

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<i>Cardiac Disorders</i>					
	palpitations*	tachycardia*, cardiac disorder	myocardial infarction [§] , torsades de pointes * [§] (see sections 4.4, 4.5 and 5.1), bradycardia, QTc extension * (see sections 4.4, 4.5 and 5.1)		
<i>Vascular Disorders</i>					
	flushes*	hypertension*, blushing, becoming red, abnormal bleeding (such as gastrointestinal bleeding) *, haematuria	Peripheral Ischaemia		
<i>Respiratory, Thoracic, and Mediastinal Disorders</i>					
	yawning*	bronchospasm* , dyspnoea, epistaxis*	hyperventilation, interstitial pulmonary disease* [§] , laryngospasm, dysphonia, stridor* [§] , hypoventilatio n, hiccups		
<i>Gastrointestinal Disorders</i>					
diarrhoea, nausea, and dry mouth	abdominal Pain* vomiting*, constipation* dyspepsia, and flatulence	oesophagitis, dysphagia, haemorrhoids, salivary hypersecretion, abnormality of tongue, eructation, melena,	mouth ulcers, pancreatitis* [§] , hematochezia, ulcers on tongue and stomatitis		

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		dental abnormality, glossitis			
<i>Hepatobiliary Disorders</i>					
			abnormal activity of the liver, severe disorders of hepatic function (including hepatitis, jaundice and liver failure)		
<i>Skin and Subcutaneous Tissue Disorders</i>					
	rash*, hyperhidrosis	periorbital oedema*, urticaria*, alopecia*, pruritus*, purpura*, dermatitis, dry skin, facial oedema and cold sweats	rare reports of severe side effects of the skin: e.g. Stevens-Johnson syndrome* and epidermal necrolysis*§, skin reaction*§, photosensitivity§, angioedema, abnormal hair texture, abnormal smell of skin, bullous dermatitis and follicular rash		
<i>Musculoskeletal and Connective Tissue Disorders</i>					
	myalgia, back pain, arthralgia*	osteoarthritis, muscle contractions, muscle cramps* and muscle weakness	rhabdomyolysis*§, bone abnormality		trismus*
<i>Renal and Urinary Disorders</i>					
		pollakisuria, miction disorder, urinary retention, urinary incontinence*,	hesitancy with urination*, oliguria		

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		polyuria and nocturia			
<i>Reproductive System and Breast Disorders**</i>					
ejaculation disorders	, menstrual irregularities* and erectile dysfunction	sexual dysfunction, menorrhagia, vaginal bleeding, sexual dysfunction in women	galactorrhoea*, atrophic vulvovaginitis, genital discharge, balanoposthitis*§, gynaecomastia* and priapism*, Atrophic Vulvovaginitis, Balanoposthitis, Genital Discharge, Priapism*, Galactorrhoea* Gynaecomastia,		
<i>General Disorders and Administration Site Conditions</i>					
fatigue *	chest pain*, malaise*, pyrexia*, asthenia*,	peripheral oedema*, shivering, gait disorder* and thirst	hernia and reduced tolerance of medicines		
<i>Investigations</i>					

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	weight gain*	elevated alanine aminotransferase*, elevated aspartate aminotransferase* and weight loss*	abnormal sperm and altered platelet function**§		
<i>Injury and poisoning</i>					
	injury				
<i>Surgical and medical procedures</i>					
			vasodilation procedure		
* Side effect established post marketing					
§ Frequency of side effect shown with estimated upper limit of 95% confidence interval using 'The rule of 3's'					

Withdrawal symptoms seen on discontinuation of sertraline treatment

Discontinuation of sertraline (particularly when abrupt) commonly leads to withdrawal symptoms.

Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported. 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 sections 4.2 and 4.4).

Elderly population

SSRIs or SNRIs including sertraline have been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse event (see section 4.4).

Paediatric population

In over 600 paediatric patients treated with sertraline, the overall profile of adverse reactions was generally similar to that seen in adult studies. The following adverse reactions were reported from controlled trials (n=281 patients treated with sertraline):

Very common (≥1/10): Headache (22%), insomnia (21%), diarrhoea (11%) and nausea (15%).

Common (≥1/100 to <1/10): Breast pain, mania, pyrexia, vomiting, anorexia, affect lability, aggression, agitation, nervousness, concentration disorder, dizziness, hyperkinesia, migraine, somnolence, tremor, visual disturbance, dry mouth, dyspepsia, nightmare, fatigue, urinary incontinence, rash, acne, epistaxis, flatulence.

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Uncommon ($\geq 1/1000$ to $< 1/100$): ECG QT prolonged (see sections 4.4, 4.5 and 5.1), suicide attempt, convulsion, extrapyramidal disorder, paraesthesia, depression, hallucination, purpura, hyperventilation, anaemia, abnormal liver function, alanine aminotransferase increased, cystitis, herpes simplex, otitis externa, ear pain, eye pain, mydriasis, malaise, haematuria, rash pustular, rhinitis, injury, weight decreased, muscle twitching, abnormal dreams, apathy, albuminuria, pollakiuria, polyuria, breast pain, menstrual disorder, alopecia, dermatitis, skin disorder, skin odour abnormal, urticaria, bruxism, flushing.

Frequency not known: enuresis

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9. Overdose

Toxicity

Sertraline has a margin of safety dependent on patient population and/or concomitant medication. Deaths have been reported involving overdoses of sertraline, alone or in combination with other drugs and/or alcohol. Therefore, any overdosage should be medically treated aggressively.

Symptoms

Symptoms of overdose include serotonin-mediated side-effects such as somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness. Less frequently reported was coma.

QTc prolongation / Torsades de Pointes has been reported after an overdose with sertraline. Therefore ECG monitoring recommended in all cases of sertraline overdose (see sections 4.4, 4.5 and 5.2)
5.1).

Treatment

There are no specific antidotes to Sertraline. Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with a cathartic, may be as or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended. Cardiac and other vital signs monitoring is recommended, along with

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general symptomatic and supportive measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors (SSRI), ATC code: N06 AB06

Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake in vitro, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of brain norepinephrine receptors as observed with other clinically effective antidepressants and antiobsessional drugs.

Sertraline has not demonstrated potential for abuse. In a placebo-controlled, double-blind randomized study of the comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria and abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforcer in rhesus monkeys trained to self administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

Clinical Trials

Major Depressive Disorder

A study was conducted which involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50-200 mg/day. These patients (n=295) were randomized to continuation for 44 weeks on double-blind sertraline 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo. The mean dose for completers was 70 mg/day. The % of responders (defined as those patients that did not relapse) for sertraline and placebo arms were 83.4% and 60.8%, respectively.

Post traumatic stress disorder (PTSD)

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Combined data from the 3 studies of PTSD in the general population found a lower response rate in males compared to females. In the two positive general population trials, the male and female sertraline vs. placebo responder rates were similar (females: 57.2% vs 34.5%; males: 53.9% vs 38.2%). The number of male and female patients in the pooled general population trials was 184 and 430, respectively and hence the results in females are more robust and males were associated with other baseline variables (more substance abuse, longer duration, source of trauma etc) which are correlated with decreased effect.

Cardiac electrophysiology

In a specially designed QTc study for this purpose, at steady state with supra-therapeutic exposures in healthy volunteers (treated with 400 mg / day, twice the maximum recommended daily dose) was the upper limit of the 2-sided 90% CI the time-matched least squares mean difference of QTcF between sertraline (11.666 msec) greater than the predetermined threshold of 10 msec at the time point of 4 hours after the dose. The reaction analysis of the exposures indicated a somewhat positive relationship between QTcF and plasma concentrations of sertraline [0.036 msec/ (ng/ml); p<0.0001]. Based on the model of exposure reactions, the threshold for clinically significant QTcF prolongation (i.e.for the predicted 90% CI to exceed 10msec) at least 2.6 times higher than the mean Cmax (86 ng / ml) after the highest recommended dose of sertraline (200mg/day) (see sections 4.4, 4.5, 4.8, and 4.9).

Paediatric OCD

The safety and efficacy of sertraline (50-200 mg/day) was examined in the treatment of non-depressed children (6-12 years old) and adolescent (13-17 years old) outpatients with obsessive compulsive disorder (OCD). After a one week single blind placebo lead-in, patients were randomly assigned to twelve weeks of flexible dose treatment with either sertraline or placebo. Children (6-12 years old) were initially started on a 25 mg dose. Patients randomized to sertraline showed significantly greater improvement than those randomised to placebo on the Children's Yale-Brown Obsessive Compulsive Scale CY-BOCS (p =0.005) the NIMH Global Obsessive Compulsive Scale (p=0.019), and the CGI Improvement (p =0.002) scales. In addition, a trend toward greater improvement in the sertraline group than the placebo group was also observed on the CGI Severity scale (p=0.089). For CY-BOCs the mean baseline and change from baseline scores for the placebo group was 22.25 ±6.15 and -3.4 ±0.82, respectively, while for the sertraline group, the mean baseline and change from baseline scores were 23.36 ±4.56 and -6.8 ±0.87, respectively. In a post-hoc analysis, responders, defined as patients with a 25% or greater decrease in the CY-BOCs (the primary efficacy measure) from baseline to endpoint, were 53% of sertraline-treated patients compared to 37% of placebo-treated patients (p=0.03).

Long term safety and efficacy data are lacking for this paediatric population.

Pediatric Patients

No data is available for children under 6 years of age.

5.2. Pharmacokinetic properties

Absorption

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Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg. In man, following an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of sertraline occur at 4.5 to 8.4 hours after the daily administration of the drug. Food does not significantly change the bioavailability of sertraline tablets.

Distribution

Approximately 98% of the circulating drug is bound to plasma proteins.

Biotransformation

Sertraline undergoes extensive first-pass hepatic metabolism.

Based on clinical and in-vitro data, it can be concluded that sertraline is metabolized by multiple pathways including CYP3A4, CYP2C19 (see section 4.5) and CYP2B6. Sertraline and its major metabolite desmethylsertraline are also substrate of P-glycoprotein *in-vitro*.

Elimination

The mean half-life of sertraline is approximately 26 hours (range 22-36 hours). Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation up to steady state concentrations, which are achieved after one week of once-daily dosing. The half-life of N-desmethylsertraline is in the range of 62 to 104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in faeces and urine in equal amounts. Only a small amount (<0.2%) of unchanged sertraline is excreted in the urine.

Linearity / nonlinearity

Sertraline has linear pharmacokinetic properties over a dose range of 50 to 200 mg.

Pharmacokinetics in specific patient groups

Paediatric patients with OCD

Pharmacokinetics of sertraline was studied in 29 paediatric patients aged 6-12 years old, and 32 adolescent patients aged 13-17 years old. Patients were gradual uptitrated to a 200 mg daily dose within 32 days, either with 25 mg starting dose and increment steps, or with 50 mg starting dose or increments. The 25 mg regimen and the 50 mg regimen were equally tolerated. In steady state for the 200 mg dose, the sertraline plasma levels in the 6-12 year old group were approximately 35% higher compared to the 13-17 year old group, and 21% higher compared to adult reference group. There were no significant differences between boys and girls regarding clearance. A low starting dose and titration steps of 25 mg are therefore recommended for children, especially with low bodyweight. Adolescents could be dosed like adults.

Adolescents and elderly

The pharmacokinetic profile in adolescents or elderly is not significantly different from that in adults between 18 and 65 years.

Liver function impairment

In patients with liver damage, the half life of sertraline is prolonged and AUC is increased three fold (see sections 4.2 and 4.4).

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Renal impairment

In patients with moderate-severe renal impairment, there was no significant accumulation of sertraline.

Pharmacogenomics

Plasma levels of sertraline were about 50% higher in poor metabolizers of CYP2C19 versus extensive metabolizers. The clinical meaning is not clear, and patients need to be titrated based on clinical response.

5.3. Preclinical safety data

Preclinical data does not indicate any special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenesis. Reproduction toxicity studies in animals showed no evidence of teratogenicity or adverse effects on male fertility. Observed foetotoxicity was probably related to maternal toxicity. Postnatal pup survival and body weight were decreased only during the first days after birth. Evidence was found that the early postnatal mortality was due to in-utero exposure after day 15 of pregnancy. Postnatal developmental delays found in pups from treated dams were probably due to effects on the dams and therefore not relevant for human risk.

Animal data from rodents and non-rodents does not reveal effects on fertility.

Studies in juvenile animals

A juvenile toxicology study in rats was performed, in which sertraline was administered orally male and female rats at Postnatal Days 21 through 56 (at doses of 10, 40 or 80) mg / kg / day) with a dose-free recovery phase up to Postnatal Day 196. Sexual maturation was delayed in male and female animals at different doses (male animals at 80 mg / kg and female animals ≥ 10 mg / kg). Despite this finding, there were no sertralinerelated effects on any of the male or female reproductive endpoints studied. In addition on Postnatal Days 21 to 56 dehydration, chromorrhinorrhea and reduced increase in it average body weight observed. All mentioned effects attributed to the administration of sertraline were reversible during any dose during the dose-free recovery phase of the study.

The clinical relevance of these effects, observed in rats given sertraline, is not determined.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core:

Cellulose, microcrystalline (E460)

Methylcellulose (E461)

Silica, colloidal anhydrous (E550)

Magnesium Stearate (E572)

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Coating:

Hypromellose (E464)

Hydroxypropylcellulose (E463)

Macrogol 8000 (E1521)

Titanium Dioxide (E171)

50 mg tablets: Indigo carmine (E132), lake

100 mg tablets: Ferric Oxide (Yellow Iron Oxide) (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of container

Sertraline film-coated tablets are packed in Aluminium/PVC/PVDC blisters containing 30, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

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

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Apotex Europe BV
Archimedesweg 2
2333 CN Leiden
Nederland

8. MARKETING AUTHORISATION NUMBER

50 mg: RVG 112794
100 mg: RVG 112795

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 17 januari 2014

Datum van verlenging van de vergunning: 28 oktober 2018

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 4.4 en 4.8: 20 september 2019