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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted STD Chemicals Limited Marketing Authorisations for the medicinal products Sertraline 50 mg and 100 mg Tablets (PL 36390/0037-8) on 04 July 2012. These are prescription-only medicines (POM) used to treat the symptoms of:

- depression (feelings of sadness, tearfulness, inability to sleep or enjoy life as you once used to) including the accompanying symptoms of anxiety;
- obsessive-compulsive disorder (OCD) an illness linked to anxiety in which you can become constantly troubled by persistent ideas (obsessions), that make you carry out repetitive rituals (compulsions);
- post traumatic stress disorder (PTSD) which can occur after a very emotionally traumatic experience. Some of the symptoms of PTSD may be similar to those of depression and anxiety.

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

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

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INTRODUCTION

On 04 July 2012, the MHRA granted Marketing Authorisations for the medicinal products Sertraline 50 mg and 100 mg Tablets (PL 36390/0037-8) to STD Chemicals Limited. The products are prescription-only medicines (POM) 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.
- 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.
- paediatric patients with OCD.

Clinical trials in PTSD (post traumatic stress disorder) 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 in males might on occasion be justified, but treatment should subsequently be withdrawn unless there is clear evidence of therapeutic benefit.

Sertraline is not indicated for use in children and adolescents under the age of 18 years with Major Depressive Disorder. In particular, controlled clinical studies have failed to demonstrate efficacy and do not support the use of sertraline in the treatment of children and adolescents with Major Depressive Disorder.

The applications were submitted as abridged applications according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Sertraline 50 mg and 100 mg Tablets (PL 20417/0079 and PL 20417/0078) which were originally granted Marketing Authorisations (PL 08137/0141-0142) to Neolab Limited on 27 September 2007. On 19 August 2011, the Marketing Authorisation Holder was updated by a change of ownership to Fannin (UK) Limited.

Sertraline 50 mg and 100 mg Tablets contain the active ingredient, sertraline (as sertraline hydrochloride), which is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake \textit{in vitro} and \textit{in vivo}, but is without affinity for muscarinic, serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 36390/0037-8

PROPRIETARY NAME: Sertraline 50 mg and 100 mg Tablets

ACTIVE(S): Sertraline hydrochloride

COMPANY NAME: STD Chemicals Limited

E.C. ARTICLE: Article 10c of Directive 2001/83/EC

LEGAL STATUS: POM

1. INTRODUCTION

These are abridged applications for Sertraline 50 mg and 100 mg Tablets (PL 36390/0037-8), submitted under Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to Sertraline 50 mg and 100 mg Tablets (PL 20417/0079 and PL 20417/0078), which are currently authorised to Fannin (UK) Limited after a change in authorisation holder on 19 August 2011.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Sertraline 50 mg and 100 mg Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each film-coated tablet for oral use contains 50 mg or 100 mg of the active ingredient, sertraline (as hydrochloride). The tablets are packaged in aluminium/polyvinyl chloride blisters. These are packed into cardboard cartons with a Patient Information Leaflet, in a calendar pack size of 28 tablets (2 blister strips, 14 tablets/strip).

The proposed shelf-life (3 years), with no special storage conditions, is consistent with the details registered for the cross-reference products.

2.3 Legal status

On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing Authorisation Holder/Contact Persons/Company

STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

The Qualified Person (QP) responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference products.
2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in-line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
None of the excipients contain materials of animal or human origin. This is consistent with the cross-reference products.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formula and utilise the same process as the reference products Sertraline 50 mg and 100 mg Tablets (PL 20417/0079 and PL 20417/0078).

3. EXPERT REPORTS
The applicant cross-refers to the data for Sertraline 50 mg and 100 mg Tablets (PL 20417/0079 and PL 20417/0078), to which it claims to be identical. This is acceptable.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to those for the cross-reference products.

5. SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs)
The proposed Summaries of Product Characteristics are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
PIL
The approved PIL is satisfactory and in line with the approved SmPCs. It is consistent with the details registered for the cross-reference products.

Neolab Limited have previously submitted results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, for the reference products Sertraline 50 mg and 100 mg Tablets (PL 08137/0141-0142). The results indicate that the leaflet is well-structured and organised, easy to understand, and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

As the leaflet for Sertraline 50 mg and 100 mg Tablets (PL 08137/0141-0142) and these products Sertraline 50 mg and 100 mg Tablets (PL 36390/0037-8) are considered the same, no further user testing of the leaflet for these products is necessary.
**Cartons and blister labels**

The proposed artwork is consistent with the artwork registered for the cross-reference products and complies with statutory requirements. In line with current legislation, the applicant has also included the names of the products in Braille on the outer packaging and sufficient space for a standard UK pharmacy dispensing label.

7. **CONCLUSION**

The data submitted with these applications are acceptable. The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As the applications are for identical versions of already authorised products, it is not expected that environmental exposure will increase following approval of the marketing authorisations for the proposed products.

The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has not submitted a Risk Management Plan (RMP). As the applications are for identical versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active ingredient is well-established.

The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for these applications.

EFFICACY
These applications are identical to previously granted applications for Sertraline 50 mg and 100 mg Tablets (PL 20417/0079 and PL 20417/0078). No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with that for Sertraline 50 mg and 100 mg Tablets (PL 20417/0079 and PL 20417/0078). The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sertraline hydrochloride is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.
SERTRALINE 50 MG TABLETS
SERTRALINE 100 MG TABLETS
PL 36390/0037-8

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 19 May 2011.
2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 10 June 2011.
3 Following assessment of the applications, the MHRA requested further information relating to the dossier on 12 October 2011, 24 February 2012 and 02 April 2012.
4 The applicant responded to the MHRA’s request, providing further information on 31 October 2011, 26 March 2012, and 13 April 2012
5 Following assessment, the applications were granted on 04 July 2012.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Sertraline 50 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg sertraline (as hydrochloride).
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White capsular shaped tablet with a breakline and ‘SRN 50’ embossed on one side and ‘NEO’ embossed on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic 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 trials 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 in males might on occasion be justified, but treatment should subsequently be withdrawn unless there is clear evidence of therapeutic benefit.

Sertraline is not indicated for use in children and adolescents under the age of 18 years with Major Depressive Disorder. In particular, controlled clinical studies have failed to demonstrate efficacy and do not support the use of sertraline in the treatment of children and adolescents with Major Depressive Disorder (See sections 4.3, Contra-indications and 4.8, Undesirable effects).

4.2 Posology and method of administration
For oral administration.
Sertraline should be given as a single daily dose. Sertraline 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 50mg 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 50mg/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.

The efficacy and safety of sertraline in children and adolescents under the age of 18 years with Major Depressive Disorder have not been established. Controlled clinical studies failed to demonstrate efficacy and do not support the use of sertraline in the treatment of children and adolescents with Major Depressive Disorder (see Sections 4.3, Contra-indications and 4.8, Undesirable effects).

**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.

### 4.3 Contraindications

Sertraline is contra-indicated in patients with a known hypersensitivity to sertraline.

Monoamine oxidase inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA) moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Sertraline should not be used in combination with a MAOI. Sertraline may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 14 days should elapse after discontinuing sertraline treatment before starting a MAOI or RIMA.

Use in hepatic impairment: There is insufficient clinical experience in patients with significant hepatic dysfunction and accordingly sertraline should not be used in such patients.

Concomitant use in patients taking pimozide is contra-indicated (see Section 4.5 - Interactions with other Medicinal Products and other forms of Interaction).

Sertraline should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder. (See Section 4.8, Undesirable effects).
4.4 Special warnings and precautions for use

Monoamine oxidase inhibitors: See 'Contra-indications'.

Use in patients with renal or hepatic impairment: As with many other medications, sertraline should be used with caution in patients with renal and hepatic impairment (see 'Contra-indications').

Since sertraline is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 20-50ml/min) or severe renal impairment (creatinine clearance <20ml/min), single dose pharmacokinetic parameters were not significantly different compared with controls. However, steady state pharmacokinetics of sertraline have not been adequately studied in this patient population and caution is advised when treating patients with renal impairment.

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 three-fold greater AUC and Cmax in comparison with 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 should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.

The following special warnings and precautions apply to the therapeutic class of SSRIs (Selective Serotonin Re-uptake Inhibitors).

Paradoxical anxiety:
Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with antidepressants. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of an anxiogenic effect (see section 4.2 Posology and method of administration).

Seizures:
The medicinal product should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency.

Mania:
SRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

Diabetes:
In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Suicide/suicidal thoughts or clinical worsening:
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 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.

**Hyponatraemia:**
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of SSRIs and generally resolves on discontinuation of therapy. Caution should be exercised in patients at risk, such as elderly, cirrhotic patients or patients concomitantly treated with medications known to cause hyponatraemia.

**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 oral anticoagulants, with 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), ticlopidine and dipyridamole) and in patients with known bleeding tendencies.

**ECT (electroconvulsive therapy):**
There is limited clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advisable.

**Monoamine oxidase inhibitors (MAOIs):**
The combination of sertraline with MAOIs (including reversible/selective) MAOIs is contraindicated due to the risk of onset of a serotonin syndrome (see section 4.3 Contra-indications).

**Serotonin syndrome:**
Caution is advisable if sertraline is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan. In rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

**St. John’s Wort:**
Concomitant use of SSRIs and herbal remedies containing St. John’s Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see section 4.5 Interactions with other medicaments and other forms of interaction).

**Withdrawal reactions:**
When stopping therapy with sertraline, the dose should be gradually reduced over a period time in order to avoid possible withdrawal reactions.

**Use in the elderly:** 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.

**Use in Children:** More than 250 paediatric OCD patients have been exposed to sertraline in completed and ongoing studies. The safety profile of sertraline in these paediatric studies is comparable to that observed in the adult OCD studies. The efficacy of sertraline in paediatric patients with depression or panic disorder has not been demonstrated in controlled trials. Safety
and effectiveness in paediatric patients below the age of 6 have not been established. There is limited knowledge with respect to an effect on sexual development in children.

4.5 Interaction with other medicinal products and other forms of interaction

**Monoamine oxidase inhibitors:** See 'Contra-indications'.

**Centrally active medication:** Caution is advised if sertraline is administered with other centrally active medication. In particular, SSRIs have the potential to interact with tricyclic antidepressants leading to an increase in plasma levels of the tricyclic antidepressant. A possible mechanism for this interaction is the inhibitory effect of SSRIs on the CYP2D6 isoenzyme. There is variability among the SSRIs in the extent to which they inhibit the activity of CYP2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered drug. In formal interaction studies, chronic dosing with sertraline 50mg daily showed minimal elevation (mean 23-37%) of steady state plasma desipramine levels (a marker of CYP2D6 isoenzyme activity).

**Pimozide:** Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2mg) with sertraline coadministration. These increased levels were not associated with any changes in ECG. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant of pimozide and sertraline is contra-indicated.

**Alcohol:** In 11 healthy subjects administered sertraline (200mg daily) for 9 days, there was no adverse effect on cognitive or psychomotor performance relative to placebo, following a single dose of 500mg/kg alcohol. However, the concomitant use of sertraline and alcohol in depressed patients is not recommended.

**Lithium and Tryptophan:** In placebo-controlled trials in normal volunteers, the co-administration of sertraline and lithium did not significantly alter lithium pharmacokinetics.

Co-administration of sertraline with lithium did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. There have been other reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of SSRIs with these drugs should be undertaken with caution.

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

Until further data are available, serotonergic drugs, such as tramadol, sumatriptan or fenfluramine, should not be used concomitantly with sertraline, due to a possible enhancement of 5-HT associated effects.

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

**Drugs that affect platelet function, such as NSAIDs:** See 'Special warnings and special precautions for use (Haemorrhage)'.

**Other drug interactions:** Since sertraline is bound to plasma proteins, the potential of sertraline to interact with other plasma protein bound drugs should be borne in mind.

Formal drug interaction studies have been performed with sertraline. Co-administration of sertraline (200 mg daily) with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters. 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 with sertraline (200mg daily) was observed with glibenclamide or digoxin.
Co-administration of sertraline (200mg daily) with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Sertraline (200mg daily), did not potentiate the effects of carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects.

4.6 Pregnancy and lactation

Pregnancy:
Although animal studies did not provide any evidence of teratogenicity, the safety of sertraline during human pregnancy has not been established. As with all drugs sertraline should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

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:
Sertraline is known to be excreted in breast milk. Its effects on the nursing infant have not yet been established. If treatment with sertraline is considered necessary, discontinuation of breast feeding should be considered.

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.

4.7 Effects on ability to drive and use machines

Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However, since antidepressant or antiobsessional drugs may impair the abilities required to perform potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly. Sertraline should not be administered with benzodiazepines or other tranquillizers in patients who drive or operate machinery.

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).

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<th>Frequency not Known</th>
<th>Very rare (&lt;1/10000)</th>
<th>Rare (≥1/10000 to &lt;1/1000)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Very Common (≥1/10)</th>
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### Infections and Infestations

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<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
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<td>Upper Respiratory Tract Infection, Rhinitis</td>
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### Neoplasms benign, malignant (including cysts and polyps)

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### Blood and lymphatic system disorders

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<th>Very Common (≥1/10)</th>
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</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>Leucopenia, Thrombocytopenia</td>
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### Immune system disorders

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<tbody>
<tr>
<td></td>
<td>Anaphylactoid Reaction, Allergic Reaction, Allergy</td>
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### Endocrine disorders

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<th>Endocrine disorders</th>
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<tbody>
<tr>
<td></td>
<td>Hyper-prolactinaemia, Hypothyroidism and syndrome of inappropriate ADH secretion</td>
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### Metabolism and Nutrition Disorders

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<tr>
<th>Metabolism and Nutrition Disorders</th>
<th>Frequency Not Known</th>
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<th>Common (≥1/100 to &lt;1/10)</th>
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</thead>
<tbody>
<tr>
<td>Anorexia, Increased Appetite*</td>
<td>Hyponatremia</td>
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<tr>
<td>Hypercholesterolaemia, Hypoglycaemia</td>
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### Psychiatric Disorders

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<tr>
<th>Psychiatric Disorders</th>
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<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Very Common (≥1/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia (19%)</td>
<td>Hallucination*, Euphoric Mood*, Apathy, Thinking Abnormal</td>
<td>Conversion Disorder, Drug Dependence, Psychotic disorder*, Aggression*, Paranoia, Suicidal Ideation/behaviour***, Sleep Walking, Premature Ejaculation</td>
<td></td>
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<td></td>
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<tr>
<td>Depression*, Depersonalisation, Nightmare, Anxiety*, Agitation*, Nervousness, Libido Decreased*, Bruxism</td>
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<tr>
<td>Libido Decreased*, Bruxism</td>
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<td>Libido Decreased*, Bruxism</td>
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### MHRA PAR – Sertraline 50 mg and 100 mg Tablets (PL 36390/0037-8)

MHRA PAR – Sertraline 50 mg and 100 mg Tablets (PL 36390/0037-8)
<table>
<thead>
<tr>
<th>Frequency</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Rare (≥1/10000 to &lt;1/1000)</th>
<th>Very rare (≤1/10000)</th>
<th>Frequency not Known</th>
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<tbody>
<tr>
<td><strong>Nervous System Disorders</strong></td>
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<tr>
<td>Dizziness (11%)</td>
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<td>Movement Disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, teeth grinding or gait abnormalities), Syncope. Also reported were signs and symptoms associated with Serotonin Syndrome or Neuroleptic Malignant Syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia. Akathesia and psychomotor restlessness (see section 4.4).</td>
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<tr>
<td>Somnolence (13%)</td>
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<tr>
<td><strong>Eye Disorders</strong></td>
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<tr>
<td>Visual Disturbance</td>
<td></td>
<td>Glaucoma, Lacrimal Disorder, Scotoma, Diplopia, Photophobia, Hyphaema, Mydriasis*</td>
<td></td>
<td></td>
<td></td>
<td>Vision Abnormal</td>
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<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
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<tr>
<td>Tinnitus*</td>
<td></td>
<td>Ear Pain</td>
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<tr>
<td><strong>Cardiac Disorders</strong></td>
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<tr>
<td>Palpitations*</td>
<td></td>
<td>Tachycardia</td>
<td>Myocardial Infarction, Bradycardia, Cardiac Disorder</td>
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<tr>
<td>Very Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very rare</td>
<td>Frequency not Known</td>
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</table>

**Vascular Disorders**

- Hot flush*
- Hypertension*, Flushing
- Peripheral Ischaemia
- Abnormal Bleeding (such as epistaxis, gastrointestinal bleeding or haematuria)

**Respiratory, Thoracic, and Mediastinal Disorders**

- Yawning*
- Bronchospasm*, Dyspnoea, Epistaxis
- Laryngospasm, Hyperventilation, Hypoventilation, Stridor, Dysphonia, Hiccups

**Gastrointestinal Disorders**

- Diarrhoea (18%), Nausea (24%), Dry Mouth (14%)
- Abdominal Pain*, Vomiting*, Constipation*, Dyspepsia, Flatulence
- Oesophagitis, Dysphagia, Haemorrhoids, Salivary Hypersecretion, Tongue Disorder, Eructation
- Melaena, Haematochezia, Stomatitis, Tongue ulceration, Tooth Disorder, Glossitis, Mouth Ulceration
- Pancreatitis

**Hepatobiliary Disorders**

- Hepatic Function Abnormal
- Serious liver events (including hepatitis, jaundice and liver failure)

**Skin and Subcutaneous Tissue Disorders**

- Rash*, Hyperhidrosis
- Periorbital Oedema*, Purpura*, Alopecia*, Cold Sweat, Dry skin, Urticaria*
- Dermatitis, Dermatitis Bullous, Rash Follicular, Hair Texture Abnormal, Skin Odour Abnormal
- Rare reports of severe cutaneous adverse reactions (SCAR): e.g. Stevens-Johnson syndrome and epidermal necrolysis, Angioedema, Face Oedema, Photosensitivity, Skin Reaction, Pruritus

**Musculoskeletal and Connective Tissue Disorders**

- Myalgia
- Osteoarthritis, Muscular Weakness, Back Pain, Muscle Twitching
- Bone Disorder
- Arthralgia, Muscle Cramps
<table>
<thead>
<tr>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Rare (≥1/10000 to &lt;1/1000)</th>
<th>Very rare (&lt;1/10000)</th>
<th>Frequency not Known</th>
</tr>
</thead>
</table>

Renal and Urinary Disorders

- Nocturia, Urinary Retention*, Polyuria, Pollakiuria, Micturition disorder
- Oliguria, Urinary Incontinence*, Urinary Hesitation

Reproductive System and Breast Disorders**

- Ejaculation Failure (14%)
- Sexual Dysfunction, Erectile Dysfunction
- Vaginal Haemorrhage, Female Sexual Dysfunction
- Menorrhagia, Atrophic Vulvovaginitis, Balanoposthitis, Genital Discharge, Priapism*, Galactorrhoea*
- Gynaecomastia, Menstrual Irregularities

General Disorders and Administration Site Conditions

- Fatigue (10%)*
- Chest Pain*
- Malaise*, Chills, Pyrexia*, Asthenia*, Thirst
- Hernia, Injection Site Fibrosis, Drug Tolerance Decreased, Gait Disturbance, Unevaluable Event
- Oedema Peripheral

Investigations

- Weight Decreased*, Weight Increased*
- Alanine Aminotransferase Increased*, Aspartate Aminotransferase Increased*, Semen Abnormal
- Abnormal Clinical Laboratory Results, Altered Platelet Function, Increased Serum Cholesterol

Injury and poisoning

- Injury

Surgical and medical procedures

- Vasodilation Procedure

* If adverse experience occurred in depression, OCD, panic disorder, PTSD and social anxiety disorder, body term reclassified by depression studies body term.

† One case of neoplasm was reported in one patient receiving sertraline compared with no cases in the placebo arm.

* these adverse reactions also occurred in postmarketing experience

** the denominator uses the number of patients in that sex group-combined: sertraline (1118 males, 1424 females) placebo (926 males, 1219 females)

For OCD, short term, 1-12 week studies only

*** Cases of suicidal ideation and suicidal behaviours have been reported during sertraline therapy or early after treatment discontinuation (see section 4.4).

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): Chest pain, mania, pyrexia, vomiting, anorexia, affect lability,
aggression, agitation, nervousness, disturbance in attention, dizziness, hyperkinesia, migraine,
somnolence, tremor, visual disturbance, dry mouth, dyspepsia, nightmare, fatigue, urinary
incontinence, rash, acne, epistaxis, flatulence.

Uncommon (≥1/1000 to <1/100): ECG QT prolonged, suicide attempt, convulsion, extrapyramidal
disorder, paraesthesia, depression, hallucination, purpura, hyperventilation, anaemia, hepatic
function abnormal, 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 SSRs and TCAs. The mechanism leading to
this risk is unknown.

4.9 Overdose
On the evidence available, sertraline has a wide margin of safety in overdose. Overdoses of
sertraline alone of up to 8g have been reported. Deaths involving overdoses of sertraline in
combination with other drugs and/or alcohol have been reported. Therefore, any overdosage
should be treated aggressively.

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.

No specific therapy is recommended and there are no specific antidotes to sertraline. Establish and
maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may
be used with sorbitol, may be as or more effective than emesis or lavage, and should be
considered in treating overdose. Cardiac and vital signs monitoring is recommended along with
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
ATC code: N06A B06 (Selective serotonin reuptake inhibitor).

Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake in vitro and in vivo, but is without affinity for muscarinic, serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors.

Sertraline is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals.

Unlike tricyclic antidepressants, no weight gain is observed with treatment for depression.

Sertraline has not been observed to produce physical or psychological dependence.

Sertraline has been evaluated in paediatric OCD patients aged 6 to 17 in a 12 week placebo-controlled study. Therapy for paediatric OCD patients (aged 6-12) commenced at 25mg/day increasing to 50mg/day after 1 week. Side-effects which occurred significantly more frequently with sertraline than placebo were: headache, insomnia, agitation [6-12 years]; insomnia, anorexia, tremor [13-17 years].

There is limited evidence of efficacy and safety beyond 12 weeks of treatment.

5.2 Pharmacokinetic properties
Sertraline exhibits dose proportional pharmacokinetics over a range of 50-200mg. After oral administration of sertraline in man, peak blood levels occur at about 4.5 - 8.4 hours. Daily doses of sertraline achieve steady-state after one week. Sertraline has a plasma half-life of approximately 26 hours with a mean half-life for young and elderly adults ranging from 22-36 hours. Sertraline is approximately 98% bound to plasma proteins. The principal metabolite, N-desmethylsertraline, is inactive in in vivo models of depression and has a half-life of approximately 62-104 hours.

Sertraline and N-desmethylsertraline are both extensively metabolised 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.

The pharmacokinetics of sertraline in paediatric OCD patients have been shown to be comparable with adults (although paediatric patients metabolise sertraline with slightly greater efficiency). However, lower doses may be advisable for paediatric patients given their lower body weights (especially 6-12 years), in order to avoid excessive plasma levels.

A clear relationship between sertraline concentration and the magnitude of therapeutic response has not been established. The pharmacokinetics of sertraline in elderly patients are similar younger adults.

Food does not significantly change the bioavailability of Sertraline tablets.

5.3 Preclinical safety data
Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective.

Animal data from rodents and non-rodsents does not reveal effects on fertility.
### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet cores:**  
- Microcrystalline cellulose  
- Maize starch  
- Sodium starch glycolate (Type A)  
- Magnesium stearate

**Film coating:**  
- Titanium dioxide (E171)  
- Hypromellose  
- Macrogol 6000

#### 6.2 Incompatibilities

None.

#### 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

Calendar packs of 28 tablets. Aluminium/PVC blister strips, 14 tablets/strip, 2 strips in a carton box.

#### 6.6 Special precautions for disposal

No special requirements.

---

### MARKETING AUTHORISATION HOLDER

STD Chemicals Limited,  
Hillbrow House,  
Hillbrow Road,  
Esher,  
Surrey,  
KT10 9NW

### MARKETING AUTHORISATION NUMBER(S)

PL 36390/0037

### DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/07/2012

### DATE OF REVISION OF THE TEXT

04/07/2012
1 NAME OF THE MEDICINAL PRODUCT
Sertraline 100 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg sertraline (as hydrochloride).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White capsular shaped tablet with ‘SRN 100’ embossed on one side and ‘NEO’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic 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 trials 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 in males might on occasion be justified, but treatment
should subsequently be withdrawn unless there is clear evidence of therapeutic benefit.

Sertraline is not indicated for use in children and adolescents under the age of 18 years with Major
Depressive Disorder. In particular, controlled clinical studies have failed to demonstrate efficacy
and do not support the use of sertraline in the treatment of children and adolescents with Major
Depressive Disorder (See sections 4.3, Contra-indications and 4.8, Undesirable effects).

4.2 Posology and method of administration
For oral administration.

Sertraline should be given as a single daily dose. Sertraline 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
tolerability 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 50mg/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.

The efficacy and safety of sertraline in children and adolescents under the age of 18 years with Major Depressive Disorder have not been established. Controlled clinical studies failed to demonstrate efficacy and do not support the use of sertraline in the treatment of children and adolescents with Major Depressive Disorder (see Sections 4.3, Contra-indications and 4.8, Undesirable effects).

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.

4.3 Contraindications
Sertraline is contra-indicated in patients with a known hypersensitivity to sertraline.

Monoamine oxidase inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI seleagine and the reversible MAOI (RIMA) moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Sertraline should not be used in combination with a MAOI. Sertraline may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 14 days should elapse after discontinuing sertraline treatment before starting a MAOI or RIMA.

Use in hepatic impairment: There is insufficient clinical experience in patients with significant hepatic dysfunction and accordingly sertraline should not be used in such patients.

Concomitant use in patients taking pimozide is contra-indicated (see Section 4.5 - Interactions with other Medicinal Products and other forms of Interaction).

Sertraline should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder. (See Section 4.8, Undesirable effects).
4.4 Special warnings and precautions for use

Monoamine oxidase inhibitors: See 'Contra-indications'.

Use in patients with renal or hepatic impairment: As with many other medications, sertraline should be used with caution in patients with renal and hepatic impairment (see 'Contra-indications').

Since sertraline is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 20-50ml/min) or severe renal impairment (creatinine clearance <20ml/min), single dose pharmacokinetic parameters were not significantly different compared with controls. However, steady state pharmacokinetics of sertraline have not been adequately studied in this patient population and caution is advised when treating patients with renal impairment.

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 three-fold greater AUC and Cmax in comparison with 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 should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment.

The following special warnings and precautions apply to the therapeutic class of SSRIs (Selective Serotonin Re-uptake Inhibitors).

Paradoxical anxiety:
Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with antidepressants. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of an anxiogenic effect (see section 4.2 Posology and method of administration).

Seizures:
The medicinal product should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency.

Mania:
SRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

Diabetes:
In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Suicide/suicidal thoughts or clinical worsening:
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 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.

**Hyponatraemia:**
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of SSRIs and generally resolves on discontinuation of therapy. Caution should be exercised in patients at risk, such as elderly, cirrhotic patients or patients concomitantly treated with medications known to cause hyponatraemia.

**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 oral anticoagulants, with 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), ticlopidine and dipyridamole) and in patients with known bleeding tendencies.

**ECT (electroconvulsive therapy):**
There is limited clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advisable.

**Monoamine oxidase inhibitors (MAOIs):**
The combination of sertraline with MAOIs (including reversible/ selective) MAOIs is contraindicated due to the risk of onset of a serotonin syndrome (see section 4.3 Contraindications).

**Serotonin syndrome:**
Caution is advisable if sertraline is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan. In rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

**St. John’s Wort:**
Concomitant use of SSRIs and herbal remedies containing St. John’s Wort (Hypericum perforatum) may result in an increased incidence of adverse reactions (see section 4.5 Interactions with other medicaments and other forms of interaction).

**Withdrawal reactions:**
When stopping therapy with sertraline, the dose should be gradually reduced over a period time in order to avoid possible withdrawal reactions.

**Use in the elderly:** 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.

**Use in Children:** More than 250 paediatric OCD patients have been exposed to sertraline in completed and ongoing studies. The safety profile of sertraline in these paediatric studies is comparable to that observed in the adult OCD studies. The efficacy of sertraline in paediatric patients with depression or panic disorder has not been demonstrated in controlled trials. Safety and effectiveness in paediatric patients below the age of 6 have not been established. There is limited knowledge with respect to an effect on sexual development in children.
4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors: See 'Contra-indications'.

Centrally active medication: Caution is advised if sertraline is administered with other centrally active medication. In particular, SSRIs have the potential to interact with tricyclic antidepressants leading to an increase in plasma levels of the tricyclic antidepressant. A possible mechanism for this interaction is the inhibitory effect of SSRIs on the CYP2D6 isoenzyme. There is variability among the SSRIs in the extent to which they inhibit the activity of CYP2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered drug. In formal interaction studies, chronic dosing with sertraline 50mg daily showed minimal elevation (mean 23-37%) of steady state plasma desipramine levels (a marker of CYP2D6 isoenzyme activity).

Pimozide: Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2mg) with sertraline coadministration. These increased levels were not associated with any changes in ECG. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant of pimozide and sertraline is contra-indicated.

Alcohol: In 11 healthy subjects administered sertraline (200mg daily) for 9 days, there was no adverse effect on cognitive or psychomotor performance relative to placebo, following a single dose of 500mg/kg alcohol. However, the concomitant use of sertraline and alcohol in depressed patients is not recommended.

Lithium and Tryptophan: In placebo-controlled trials in normal volunteers, the co-administration of sertraline and lithium did not significantly alter lithium pharmacokinetics.

Co-administration of sertraline with lithium did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. There have been other reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of SSRIs with these drugs should be undertaken with caution.

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

Until further data are available, serotonergic drugs, such as tramadol, sumatriptan or fenfluramine, should not be used concomitantly with sertraline, due to a possible enhancement of 5-HT associated effects.

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

Drugs that affect platelet function, such as NSAIDs: See 'Special warnings and special precautions for use (Haemorrhage)'.

Other drug interactions: Since sertraline is bound to plasma proteins, the potential of sertraline to interact with other plasma protein bound drugs should be borne in mind.

Formal drug interaction studies have been performed with sertraline. Co-administration of sertraline (200 mg daily) with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters. 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 with sertraline (200mg daily) was observed with glibenclamide or digoxin.

Co-administration of sertraline (200mg daily) with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown.
Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Sertraline (200mg daily), did not potentiate the effects of carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects.

4.6 Pregnancy and lactation

Pregnancy:
Although animal studies did not provide any evidence of teratogenicity, the safety of sertraline during human pregnancy has not yet been established. As with all drugs sertraline should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

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:
Sertraline is known to be excreted in breast milk. Its effects on the nursing infant have not yet been established. If treatment with sertraline is considered necessary, discontinuation of breast feeding should be considered.

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.

4.7 Effects on ability to drive and use machines

Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However, since antidepressant or antiobsessional drugs may impair the abilities required to perform potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly. Sertraline should not be administered with benzodiazepines or other tranquillizers in patients who drive or operate machinery.

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).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Very Common (≥1/10 to &lt;1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Rare (≥1/10000 to &lt;1/1000)</th>
<th>Very rare (&lt;1/10000)</th>
<th>Frequency not Known</th>
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<td>Infections and Infections</td>
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<td>Neoplasms benign, malignant (including cysts and polyps)</td>
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<td>Metabolism and Nutrition Disorders</td>
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<td>Psychiatric Disorders</td>
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</table>

MHRA PAR – Sertraline 50 mg and 100 mg Tablets (PL 36390/0037-8)
<table>
<thead>
<tr>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Rare (≥1/10000 to &lt;1/1000)</th>
<th>Very rare (&lt;1/10000)</th>
<th>Frequency not Known</th>
</tr>
</thead>
</table>

**Nervous System Disorders**

Dizziness (11%), Somnolence (13%), Headache (21%)*  
Paraesthesia*, Tremor, Hypertonia, Dysgeusia, Disturbance in Attention,  
Convulsion*, Muscle Contractions Involuntary*, Coordination Abnormal, Hyperkinesia, Amnesia, Hypoaesthesia*, Speech Disorder, Dizziness Postural, Migraine*  
Coma*, Choreaathetosis, Dyskinesia, Hypraesthesia, Sensory Disturbance  
Movement Disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, teeth grinding or gait abnormalities), Syncope. Also reported were signs and symptoms associated with Serotonin Syndrome or Neuroleptic Malignant Syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia. Akathisia and psychomotor restlessness (see section 4.4).

**Eye Disorders**

Visual Disturbance  
Glaucoma, Lacrimal Disorder, Scotoma, Diplopia, Photophobia, Mydriasis*  
Vision Abnormal

**Ear and Labyrinth Disorders**

Tinnitus*  
Ear Pain

**Cardiac Disorders**

Palpitations*  
Tachycardia  
Myocardial Infarction, Bradycardia, Cardiac Disorder
<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Frequency not Known</th>
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<tbody>
<tr>
<td>(≥1/10 to &lt;1/10)</td>
<td>(≥1/100 to &lt;1/1000)</td>
<td>(≥1/1000 to &lt;1/100)</td>
<td>(≥1/10000 to &lt;1/1000)</td>
<td>(&lt;1/10000)</td>
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</tbody>
</table>

**Vascular Disorders**

- Hot flush*
- Hypertension*, Flushing
- Peripheral Ischaemia
- Abnormal Bleeding (such as epistaxis, gastrointestinal bleeding or haematuria)

**Respiratory, Thoracic, and Mediastinal Disorders**

- Yawning*
- Bronchospasm*, Dyspnoea, Epistaxis
- Laryngospasm, Hyperventilation, Hypoventilation, Stridor, Dysphonia, Hiccups

**Gastrointestinal Disorders**

- Diarrhoea (18%), Nausea (24%), Dry Mouth (14%)
- Abdominal Pain*, Vomiting*, Constipation*, Dyspepsia, Flatulence
- Oesophagitis, Dysphagia, Haemorrhoids, Salivary Hypersecretion, Tongue Disorder, Eruetation
- Melaena, Haematochezia, Stomatitis, Tongue ulceration, Tooth Disorder, Glossitis, Mouth Ulceration
- Pancreatitis

**Hepatobiliary Disorders**

- Hepatic Function Abnormal
- Serious liver events (including hepatitis, jaundice and liver failure)

**Skin and Subcutaneous Tissue Disorders**

- Rash*, Hyperhidrosis
- Periorbital Oedema*, Purpura*, Alopecia*, Cold Sweat, Dry skin, Urticaria*
- Dermatitis, Dermatitis Bullous, Rash Follicular, Hair Texture Abnormal, Skin Odour Abnormal
- Rare reports of severe cutaneous adverse reactions (SCAR): e.g. Stevens-Johnson syndrome and epidermal necrolysis, Angioedema, Face Oedema, Photosensitivity, Skin Reaction, Pruritus

**Musculoskeletal and Connective Tissue Disorders**

- Myalgia
- Osteoarthritis, Muscular Weakness, Back Pain, Muscle Twitching
- Bone Disorder
- Arthralgia, Muscle Cramps
<table>
<thead>
<tr>
<th>Very Common (≥1/100 to &lt;1/10)</th>
<th>Common (≥1/1000 to &lt;1/100)</th>
<th>Uncommon (≥1/10000 to &lt;1/1000)</th>
<th>Rare (≥1/100000 to &lt;1/10000)</th>
<th>Very rare (&lt;1/10000)</th>
<th>Frequency not Known</th>
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<tbody>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Nocturia, Urinary Retention*, Polyuria, Pollakiuria, Micturition disorder</td>
<td>Oliguria, Urinary Incontinence*, Urinary Hesitation</td>
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<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td><strong>Ejaculation Failure (14%)</strong></td>
<td>Sexual Dysfunction, Erectile Dysfunction</td>
<td>Vaginal Haemorrhage, Female Sexual Dysfunction</td>
<td>Menorrhagia, Atrophic Vulvovaginitis, Balanoposthitis, Genital Discharge, Priapism*, Galactorrhoea*</td>
<td>Gynaecomastia, Menstrual Irregularities</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td><strong>Fatigue (10%)</strong>*</td>
<td>Chest Pain*</td>
<td>Malaise*, Chills, Pyrexia*, Asthenia*, Thirst</td>
<td>Hernia, Injection Site Fibrosis, Drug Tolerance Decreased, Gait Disturbance, Unevaluable Event</td>
<td>Oedema Peripheral</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Weight Decreased*, Weight Increased*</td>
<td>Alanine Aminotransferase Increased*, Aspartate Aminotransferase Increased*, Semen Abnormal</td>
<td></td>
<td></td>
<td>Abnormal Clinical Laboratory Results, Altered Platelet Function, Increased Serum Cholesterol</td>
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<tr>
<td><strong>Injury and poisoning</strong></td>
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<td><strong>Surgical and medical procedures</strong></td>
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If adverse experience occurred in depression, OCD, panic disorder, PTSD and social anxiety disorder, body term reclassified by depression studies body term.
† One case of neoplasm was reported in one patient receiving sertraline compared with no cases in the placebo arm.
* these adverse reactions also occurred in postmarketing experience
** the denominator uses the number of patients in that sex group-combined: sertraline (1118 males, 1424 females) placebo (926 males, 1219 females)
For OCD, short term, 1-12 week studies only
*** Cases of suicidal ideation and suicidal behaviours have been reported during sertraline therapy or early after treatment discontinuation (see section 4.4).

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):** Chest pain, mania, pyrexia, vomiting, anorexia, affect lability, aggression, agitation, nervousness, disturbance in attention, dizziness, hyperkinesia, migraine, somnolence, tremor, visual disturbance, dry mouth, dyspepsia, nightmare, fatigue, urinary incontinence, rash, acne, epistaxis, flatulence.

**Uncommon (≥1/1000 to <1/100):** ECG QT prolonged, suicide attempt, convulsion, extrapyramidal disorder, paraesthesia, depression, hallucination, purpura, hyperventilation, anaemia, hepatic function abnormal, 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 SSRs and TCAs. The mechanism leading to this risk is unknown.

**4.9 Overdose**
On the evidence available, sertraline has a wide margin of safety in overdose. Overdoses of sertraline alone of up to 8g have been reported. Deaths involving overdoses of sertraline in combination with other drugs and/or alcohol have been reported. Therefore, any overdosage should be treated aggressively.

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.

No specific therapy is recommended and there are no specific antidotes to sertraline. Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs monitoring is recommended along with 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
ATC code: N06A B06 (Selective serotonin reuptake inhibitor).

Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake in vitro and in vivo, but is without affinity for muscarinic, serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors.

Sertraline is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. Unlike tricyclic antidepressants, no weight gain is observed with treatment for depression.

Sertraline has not been observed to produce physical or psychological dependence.

Sertraline has been evaluated in paediatric OCD patients aged 6 to 17 in a 12 week placebo-controlled study. Therapy for paediatric OCD patients (aged 6-12) commenced at 25mg/day increasing to 50mg/day after 1 week. Side-effects which occurred significantly more frequently with sertraline than placebo were: headache, insomnia, agitation [6-12 years]; insomnia, anorexia, tremor [13-17 years].

There is limited evidence of efficacy and safety beyond 12 weeks of treatment.

5.2 Pharmacokinetic properties
Sertraline exhibits dose proportional pharmacokinetics over a range of 50-200mg. After oral administration of sertraline in man, peak blood levels occur at about 4.5 - 8.4 hours. Daily doses of sertraline achieve steady-state after one week. Sertraline has a plasma half-life of approximately 26 hours with a mean half-life for young and elderly adults ranging from 22-36 hours. Sertraline is approximately 98% bound to plasma proteins. The principal metabolite, N desmethylsertraline, is inactive in in vivo models of depression and has a half-life of approximately 62-104 hours. Sertraline and N-desmethylsertraline are both extensively metabolised 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.

The pharmacokinetics of sertraline in paediatric OCD patients have been shown to be comparable with adults (although paediatric patients metabolise sertraline with slightly greater efficiency). However, lower doses may be advisable for paediatric patients given their lower body weights (especially 6-12 years), in order to avoid excessive plasma levels.

A clear relationship between sertraline concentration and the magnitude of therapeutic response has not been established. The pharmacokinetics of sertraline in elderly patients are similar younger adults.

Food does not significantly change the bioavailability of Sertraline tablets.

5.3 Preclinical safety data
Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective.

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

6.1 List of excipients
Tablet cores:
- Microcrystalline cellulose
- Maize starch
- Sodium starch glycolate (Type A)
- Magnesium stearate

Film coating:
- Titanium dioxide (E171)
- Hypromellose
- Macrogol 6000

6.2 Incompatibilities
None.

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
Calendar packs of 28 tablets. Aluminium/PVC blister strips, 14 tablets/strip, 2 strips in a carton box.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/07/2012

10 DATE OF REVISION OF THE TEXT
04/07/2012
PATIENT INFORMATION LEAFLET

SERTRALINE 50 & 100 mg TABLETS

Read all of this leaflet carefully before you start taking this medicine.
• Keep this leaflet you need to read it again.
• If you have further questions, please ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Sertraline Tablets are and what they are used for
2. Before you take Sertraline Tablets
3. How to take Sertraline Tablets
4. Possible side effects
5. How to store Sertraline Tablets
6. Further information

1. WHAT SERTRALINE TABLETS ARE AND WHAT THEY ARE USED FOR

Sertraline is one of a group of medicines called selective serotonin reuptake inhibitors (SSRIs). These work by bringing the level of serotonin in the brain back up to normal. Low levels of serotonin are thought to cause a range of depression and related disorders.

Sertraline is used to treat symptoms of:
• depression (feeling of sadness, hopelessness, inability to sleep or enjoy life as you once used to)
• obsessive-compulsive disorder (OCD) (an illness linked to anxiety which you can become constantly troubled by persistent ideas (obsessions), that make you carry out repetitive tasks (compulsions)); post-traumatic stress disorder (PTSD) which can occur after a very emotionally traumatic experience. Some of the symptoms of PTSD may be similar to those of depression and anxiety.

2. BEFORE YOU TAKE SERTRALINE TABLETS

Do not take Sertraline Tablets if:
• you are allergic (hypersensitive) to sertraline or any of the other ingredients in the tablets (these are listed in Section 4). Further information).
• you are taking a monoamine oxidase inhibitor drug (MAOI) for depression or have stopped taking one within the last two weeks.
• Examples of MAOIs include selegiline and moclobemide.
• you are taking a medicine called pimozide (for the treatment of psychosis in elderly people).
• you have a liver disorder.
• you are a child or adolescent under 12 years suffering from depression.
• you are a child under 6 years suffering from an obsessive-compulsive disorder.

Special cases with Sertraline Tablets

Before you take Sertraline Tablets you should tell your doctor:
• if you have epilepsy or are receiving ECT (electroconvulsive therapy).
• if you suffer from diabetes, as your medication may need adjusting.
• if you have kidney problems.
• if you have a bleeding disorder.
• if you are pregnant, likely to become pregnant or you suspect you are pregnant.
• if you are breastfeeding.

Sertraline can affect the results of some blood, urine or other tests. It may not affect all tests. If you have a blood or urine test done, tell the doctor or medical staff that you are taking Sertraline Tablets.

Important information about Sertraline Tablets and thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:
• if you have previously had thoughts of killing or harming yourself.
• if you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.
• If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Taking other medicines

You should tell your doctor if you are taking or have recently taken any of the following medicines, including medicines obtained without a prescription, as they may increase or decrease the effect of your Sertraline Tablets.
• other medicines for treating depression
• a monoamine oxidase inhibitor drug (MAOI) or have stopped taking one within the last two weeks (eg selegiline and moclobemide).
• pimozide (for the treatment of schizophrenia or psychosis).
• diazepam, lithium or haloperidol for the treatment of depression, anxiety and other mental disorders.
• tricyclic antidepressants such as imipramine, desipramine and amitriptyline.
• corticosteroids, a drug used to treat diabetes.
• warfarin (used to thin the blood).
• ciclosporin used in the treatment of organ transplantation.
• non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief, including aspirin.
• serotonin uptake inhibitors such as tramadol (an analgesic), sumatriptan (for migraine) or nefazodone (an appetite suppressant).

If you think you may be pregnant, it is important to discuss this with your doctor or pharmacist as soon as possible.

It may still be all right for you to take Sertraline Tablets and your doctor will be able to decide what is suitable for you.

Taking your medicine with food and alcohol

Sertraline Tablets can be taken with or without food. Drinking alcohol while being treated with sertraline is not recommended.

Pregnancy and breast-feeding

If you are pregnant, likely to become pregnant or are breast-feeding, you must tell your doctor before taking this medicine and your doctor will decide if this medicine is right for you.

Make sure your midwife and/or doctor know you are on Sertraline Tablets. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Sertraline Tablets may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

These tablets may make you feel drowsy or affect your concentration. You should not drive or operate machinery if affected.

3. HOW TO TAKE SERTRALINE TABLETS

Method of Administration: Sertraline Tablets should be swallowed whole with a glass of water, preferably at the same time each day.

Dosage: Your doctor will decide on the right starting dose for you and any increase in the dose depending on your condition and whether you are taking any other medicines. Always take Sertraline Tablets exactly as your doctor tells you. Take any missed dose as soon as you remember. If you are not sure, the label on the carton will tell you how many tablets you should take and when.
The usual doses for Sertraline Tablets are as follows:

**Adults:**
Depression (including accompanying symptoms of anxiety) and Obsessive Compulsive Disorder
The usual starting and maintenance dose for treatment in adults is 50 mg once a day. Some patients may need a higher dose up to a maximum of 200 mg a day. Your doctor should not increase the dose by more than 50 mg per week.
Post-Traumatic Stress Disorder
The usual starting dose for treatment in adults is 25 mg once a day. After one week, this should be increased to 50 mg once a day. Response to treatment should be reviewed at intervals by your doctor and if there seems to be no evidence of benefit, the treatment should be withdrawn.

**Children and Adolescents:**
Obsessive Compulsive Disorder
Children aged 12–17 should be started at a dose of 50 mg daily.
Children aged 6–12 should be started at a dose of 25 mg once a day increasing to 50 mg daily after one week. If there is lack of response, the dose can be increased at not less than weekly intervals until your doctor will take into account the lower body weight of the child to avoid excessive dose.

Not recommended for use in children under 6 years of age.
Depression
Not recommended for use in children and adolescents under 18 years of age.

**Treatment duration**
You may not start to feel better when you first start taking this medicine. It may take up to 2–4 weeks for your symptoms to improve, so keep taking the tablets. Tell your doctor if you feel worse after starting this medication.
Even when you start to feel better you should continue to take this medicine. If you suffer from depression this may be for 4–6 months or longer. You may need to continue taking the medicine for longer if you suffer from OCD. Tell your doctor if you have taken all your tablets and you still feel unwell.

If you take more Sertraline Tablets than you should:
If you have accidentally taken more than your prescribed dose, contact your nearest casualty department or take your doctor or pharmacist immediately. Remember to take the pack and any remaining tablets with you. The most common signs and symptoms of overdose are nausea and vomiting, a forceful and rapid heartbeat, tremor, agitation and dizziness.

If you forget to take Sertraline Tablets:
It is important that you take your medicine every day. If you forget to take your medicine, just take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Sertraline Tablets:
If you stop taking Sertraline Tablets suddenly, you may experience withdrawal or discontinuation symptoms. These can include headaches, feeling dizzy, shaky, stuffy, nervous, irritable, or confused. Some people experience tingling sensations, pins and needles, burning sensations, electric shock-like sensations or they feel that they sweat more. Difficulty in sleeping and strange dreams can also occur. If you are troubled by any of these withdrawal symptoms, your doctor may advise you to reduce the amount of medicine gradually by taking smaller amounts or taking the medicine less frequently for some time before stopping the tablets completely. Do not stop taking your medicine abruptly and do not stop taking your medicine without talking to your doctor first.

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 Tablets can cause side effects although not everybody gets them. All medicines can cause allergic reactions although serious allergic reactions are very rare. If you get any of the following symptoms after taking these tablets, you should stop taking the tablets and contact your doctor immediately:

- Any sudden wheeziness, difficulty in breathing or tightness, swelling of the eyelids, face, lips or throat
- Rash or itching (especially affecting your whole body)
- Convulsions

If you develop any of the following side effects tell your doctor:

### Common side effects

- Nausea
- Feeling sick
- Diarrhoea
- Stomach upsets
- Indigestion
- Dry mouth
- Loss of appetite
- Anorexia
- Tiredness
- Headache
- Dizziness
- Insomnia
- (difficulty sleeping)
- Increased sweating
- Headache
- Feeling tense or nervous
- Muscle or joint pain

The following side effects have also been reported:

- Fever
- Rigidity, muscle stiffness
- Severe abdominal pain which may be due to pancreatitis (inflammation of the pancreas)
- Infections in the liver which can cause jaundice, a yellowing of the skin and eyes
- Psychological effects (confusion, agitation, anxiety, not being able to concentrate or think properly, panic attacks, aggression, memory loss, hallucinations, loss of feeling of identity)
- Sexual thoughts
- Abnormal vision
- Effects on the nervous system (trembling, numbness or uncontrollable twitches, jerking or writhing movements)
- Effects on the urinary and reproductive system (difficulty passing urine, changes to sexual drive or function e.g. not being able to experience orgasm, erectile dysfunction, changes to sexual function such as loss of libido)
- Effects on the skin (itching, rash)
- Increased production of milk or breast engorgement
- Rapid heartbeat and changes to blood pressure causing dizziness on standing up
- Unexplained bruising, bleeding, skin rashes, itching and sensitivity to light

The concentration of water in your blood may become lower (hyponatraemia) and may be associated with other drugs such as diuretics, or occur more commonly in the elderly or patients with liver disease. Symptoms include, nausea (feeling sick), vomiting (being sick), headaches, tiredness and confusion, muscle twitching, fits and coma.

An increased risk of bone fractures has been observed in patients taking this type of medicine.

Some medicines like sertraline may reduce the quality of sperm in animal studies. Theoretically, this could affect fertility. If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### 5. HOW TO STORE SERTRALINE TABLETS

Do not take this medicine after the expiry date shown on the carton. The expiry date is the last day of that batch.

Keep all medicines out of the reach and sight of children.

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 Tablets contain:
The active substance is sertraline (as hydrochloride). Each tablet contains 50 or 100 mg of sertraline (as hydrochloride).

The other ingredients are microcrystalline cellulose, maize starch, sodium starch glycolate (Type A), magnesium stearate, titanium dioxide (E171), hypromellose and macrogol 6000.

What Sertraline Tablets look like and the contents of the pack:
Sertraline 50 mg Tablets are white, capsule shaped, film-coated tablets, with a green line, embossed on one side with ‘SN 50’ and ‘NEO’ on the other side. Sertraline 100 mg Tablets are white, capsule shaped, film-coated tablets, with ‘SN 60’ embossed on one side and ‘NEO’ on the other side.

Your medicine is available in blister packs of 30 tablets.

The Product Licence Holder is S.D. Pharmaceuticals Ltd, Hillfarrance House, Hillfarrance Road, Esther, Surrey, KT10 9NW.

The manufacturer responsible for batch release is Novo Nordisk Ltd, 57 High Street, Oldham, Hants, RG29 1LP.
Sertraline Tablets
Each tablet contains 50 mg sertraline (as hydrochloride).

28 Tablets

MHRA PAR – Sertraline 50 mg and 100 mg Tablets (PL 36390/0037-8)  40
For oral use.

Dosage: To be taken as directed by your doctor.
Please read the enclosed leaflet carefully before use.
Keep out of the reach and sight of children.

Each tablet contains 100 mg sertraline (as hydrochloride).

28 Tablets

Distributor: Neon Ltd, 39 High Street, Odiham, Hampshire, RG29 1LE.
PL 363900038
MA Holder: STD Chemicals Ltd, Hillrow House, Hillrow Road, Esher, Surrey, KT10 9NW.