SERTRALINE 50MG TABLETS (PL 08137/0141)
SERTRALINE 100MG TABLETS (PL 08137/0142)

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TABLE OF CONTENTS

SERTRALINE 50MG TABLETS (PL 08137/0141)
SERTRALINE 100MG TABLETS (PL 08137/0142)

LAY SUMMARY

On 24th September 2007, the MHRA granted Neolab Limited Marketing Authorisations (licences) for the medicinal products Sertraline 50mg and 100mg Tablets (PL 08137/0141-2). These are prescription only medicines (POM) that are used for the treatment of the following conditions:

- The symptoms of depression (feelings of sadness, tearfulness, inability to sleep or enjoy life as you once used to) and any anxiety you may have at the same time.
- Obsessive-compulsive disorder (OCD). OCD is 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). PTSD can occur after a very emotionally traumatic experience. Some of the symptoms of PTSD are similar to depression and anxiety.

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

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

SERTRALINE 50MG TABLETS (PL 08137/0141)
SERTRALINE 100MG TABLETS (PL 08137/0142)

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Sertraline 50mg and 100mg Tablets to Neolab Limited (PL 08137/0141-2) on 24th September 2007. The products are prescription-only medicines for the treatment of:

- Symptoms of depressive illness
- Treatment of obsessive compulsive disorder
- Post traumatic stress disorder
- Major depressive disorder

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, claiming essential similarity to the original products Lustral 50mg and 100mg Tablets (PL 00057/0308-9), which have been authorised to Pfizer Limited in the UK since November 1990.

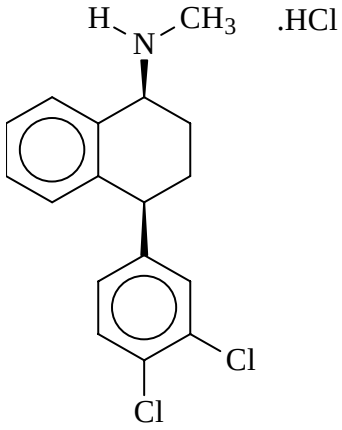
The active ingredient, sertraline, is one of a group of antidepressant or anti-obsessional medicines known as selective serotonin reuptake inhibitors (SSRIs).

PHARMACEUTICAL ASSESSMENT

Active Substance
INN/Ph.Eur name: Sertraline

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

Structural formula



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

Molecular weight: 342.73

Sertraline has no European Pharmacopoeia monograph.

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

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

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

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a retest period of 12 months when stored in a double polyethylene bag with a cardboard box at 25°C/60%RH. This is acceptable.

Other Ingredients

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, maize starch, sodium starch glycollate, magnesium stearate and water purified. The film coating consists of Opadry white (titanium dioxide, hypromellose and macrogol 6000) and purified water.

All excipients are controlled according to their European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

With the exception of magnesium stearate, none of the other ingredients use materials of animal or human origin in their production. A certificate of suitability has been provided by the manufacturers of magnesium stearate showing compliance with current guidelines concerning the minimising of transmission of TSE/BSE.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce products containing 50mg and 100mg sertraline that are tolerable and which could be considered as generic products to the originator products Lustral 50 and 100 mg Tablets.

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

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

Comparative *in vitro* dissolution profiles have been generated for the proposed and originator products with satisfactory results. Comparative impurity studies have also been undertaken.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results at pilot-scale. Additionally, a commitment has been provided that the first full-scale commercial production batches will be validated.

Finished Product Specification

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

Container-Closure System

All strengths of tablet are packaged in polyvinylchloride/aluminium blister strips in pack sizes of 28 tablets.

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

Stability of the product
Stability studies were performed on pilot-scale batches of all strengths of finished product in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 36 months, with no storage conditions.

The applicant has committed to providing stability data for the first three production-scale batches of each strength of finished product.

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

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

CONCLUSION
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products.

PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Lustral 50mg and 100mg Tablets (Pfizer Limited, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND

These are a complex and a standard abridged national applications for Sertraline 50mg and 100mg Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applications cross-refer to Lustral 50 and 100 mg Tablets (Pfizer Limited, UK), which have been authorised in the EU for more than 10 years.

2. 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).

The indications proposed are consistent with those for the originator products and are, therefore, satisfactory.

3. DOSE & DOSE SCHEDULE

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.

The dose and dose schedule proposed are consistent with those for the originator products and are, therefore, satisfactory.

4. CLINICAL PHARMACOLOGY

With the exception of the bioequivalence study comparing the applicant's 50mg tablets versus Lustral 50mg Tablets, no formal data are provided and none are required for these applications.

4.1 Bioequivalence

This was a balanced, open-label two-treatment, two-period, two-sequence, single-dose crossover trial comparing Sertraline 50mg Tablets versus Lustral 50 mg Tablets in 24 healthy volunteers. Results were as follows:

	Geometric Mean Values	**Geometric Mean Values**	**Ratio t:r**	**90% CI**
	Test	**Reference**		
C_{max}(ng/ml)	36.11	35.35	102.14	97.40-107.12
AUC_{0-t} ng.ml/h	862.18	804.16	107.22	98.69–116.48
AUC_{0-inf}	951.82	893.47	106.53	98.63-115.06
	mean values			
t_{max}	7.85	7.90		
Half-life	23.93	24.98		

Conclusion: The ratios of AUC and C_{max} test:reference had 90% confidence intervals between the guideline range 80–125% thereby satisfying the criteria for comparable bioavailability and hence bioequivalence. There were no adverse events reported.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg strength can be extrapolated to the 100mg strength tablets.

5. EFFICACY

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

6. SAFETY

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

7. EXPERT REPORTS

A clinical expert report is provided, written by an appropriately qualified Doctor. It includes a suitable review of the bioequivalence study.

8. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPCs are consistent with the approved SPCs for the originator products Lustral 50 and 100 mg Tablets and are satisfactory.

9. PATIENT INFORMATION LEAFLET (PIL)

The PIL has been provided and is consistent the SPC.

10. LABELLING

Labelling text for all strengths are satisfactory. Mock-ups of labelling intended for marketing are satisfactory and comply with current regulations.

11. APPLICATION FORM (MAA)

The MAA forms are satisfactory.

12. DISCUSSION

Bioequivalence has been satisfactorily demonstrated for the 50mg product in accordance with CPMP criteria. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg strength can be extrapolated to the 100mg strength tablets.

The SPC and PIL are consistent with those approved in the UK for the originator product Lustral 50 and 100 mg Tablets, and are satisfactory.

13. MEDICAL CONCLUSION

Marketing authorisations may be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

PRECLINICAL

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

EFFICACY

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

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT

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

SERTRALINE 50MG TABLETS (PL 08137/0141)
SERTRALINE 100MG TABLETS (PL 08137/0142)

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 19th November 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 8th December 2004
3	Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 28th November 2005 and 1st May 2007. No requests for further information were made for the clinical dossier.
4	The applicant responded to the MHRA's requests, providing further information on 30th March 2007 and 29th June 2007 for the quality dossiers.
5	The applications were determined on 24th September 2007

SERTRALINE 50MG TABLETS (PL 08137/0141)
SERTRALINE 100MG TABLETS (PL 08137/0142)

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

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 excipients, see 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 C_{max} 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:
It is general clinical experience with SSRIs that the risk of suicide may increase during the first weeks of therapy. Close monitoring of the patient during this period is important.

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.

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.

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

Side-effects which occurred significantly more frequently with sertraline than placebo in multiple dose studies were: nausea, diarrhoea/loose stools, anorexia, dyspepsia, tremor, dizziness, insomnia, somnolence, increased sweating, dry mouth and sexual dysfunction (principally ejaculatory delay in males).

The side-effect profile commonly observed in double-blind, placebo-controlled studies in patients with OCD and PTSD was similar to that observed in patients with depression.

In paediatric OCD patients, side-effects which occurred significantly more frequently with sertraline than placebo were: headache, insomnia, agitation, anorexia, tremor. Most were of mild to moderate severity.

Post-marketing spontaneous reports include the following:
Cardiovascular: Blood pressure disturbances including postural hypotension, tachycardia.

Eye disorders: Abnormal vision.

Gastro-intestinal: Vomiting, abdominal pain.

Nervous system: Amnesia, headache, drowsiness, movement disorders, paraesthesia, hypoaesthesia, depressive symptoms, hallucinations, aggressive reaction, agitation, anxiety, psychosis, depersonalisation, nervousness, panic reaction and signs and symptoms associated with serotonin syndrome which include fever, rigidity, confusion, agitation, diaphoresis, tachycardia, hypertension and diarrhoea.

There have also been reports of manic reaction, although this phenomenon may be part of the underlying disease.

Convulsions (Seizures): Sertraline should be discontinued in any patient who develops seizures (See 'Special warnings and special precautions for use').

Musculoskeletal: Arthralgia, myalgia.

Hepatic/pancreatic: Rarely, pancreatitis and serious liver events (including hepatitis, jaundice and liver failure). Asymptomatic elevations in serum transaminases (SGOT and SGPT) have been reported in association with sertraline administration (0.8 – 1.3%), with an increased risk associated with the 200mg daily dose. The abnormalities usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Renal & urinary disorders: Urinary retention.

Reproductive: Hyperprolactinemia, galactorrhoea, menstrual irregularities, anorgasmy.

Skin and allergic reactions: Rash (including rare reports of erythema multiforme, photosensitivity), angioedema, ecchymoses, pruritus and anaphylactoid reactions.

Metabolic: Rare cases of hyponatremia have been reported and appeared to be reversible when sertraline was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients, and patients taking diuretics or other medications.

Haematologic: There have been rare reports of altered platelet function and/or abnormal clinical laboratory results in patients taking sertraline. While there have been reports of thrombocytopenia, abnormal bleeding or purpura in several patients taking sertraline, it is unclear whether sertraline had a causative role. See also 'Special warnings and special precautions for use'.

General Malaise.

Other: Withdrawal reactions have been reported with Sertraline. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with sertraline should be avoided. The majority of symptoms experienced on withdrawal of sertraline are non-serious and self-limiting.

Adverse events from paediatric clinical trials: In paediatric clinical trials in depression the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: dry mouth (2.1% vs 0.5%), hyperkinesia (2.6% vs 0.5%), tremor (2.1% vs 0%), diarrhoea (9.5% vs 1.6%) vomiting (4.2% vs 1.1%), agitation (6.3% vs 1.1%), anorexia (5.3% vs 1.1%) and urinary incontinence (2.1% vs 0%). Suicidal thoughts and suicide attempts were mainly observed in clinical trials with Major Depressive Disorder.

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.

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
Neolab Limited
57 High Street
Odiham
Hants
RG29 1LF

8 MARKETING AUTHORISATION NUMBER(S)
PL 08137/0141

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/09/2007

10 DATE OF REVISION OF THE TEXT
24/09/2007

1 NAME OF THE MEDICINAL PRODUCT

Sertraline 100 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg sertraline (as hydrochloride).
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

White capsular shaped tablet with 'SRN 100' 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 C_{max} 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:
It is general clinical experience with SSRIs that the risk of suicide may increase during the first weeks of therapy. Close monitoring of the patient during this period is important.

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.

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.

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

Side-effects which occurred significantly more frequently with sertraline than placebo in multiple dose studies were: nausea, diarrhoea/loose stools, anorexia, dyspepsia, tremor, dizziness, insomnia, somnolence, increased sweating, dry mouth and sexual dysfunction (principally ejaculatory delay in males).

The side-effect profile commonly observed in double-blind, placebo-controlled studies in patients with OCD and PTSD was similar to that observed in patients with depression.

In paediatric OCD patients, side-effects which occurred significantly more frequently with sertraline than placebo were: headache, insomnia, agitation, anorexia, tremor. Most were of mild to moderate severity.

Post-marketing spontaneous reports include the following:
Cardiovascular: Blood pressure disturbances including postural hypotension, tachycardia.

Eye disorders: Abnormal vision.

Gastro-intestinal: Vomiting, abdominal pain.

Nervous system: Amnesia, headache, drowsiness, movement disorders, paraesthesia, hypoaesthesia, depressive symptoms, hallucinations, aggressive reaction, agitation, anxiety, psychosis, depersonalisation, nervousness, panic reaction and signs and symptoms associated with serotonin syndrome which include fever, rigidity, confusion, agitation, diaphoresis, tachycardia, hypertension and diarrhoea.

There have also been reports of manic reaction, although this phenomenon may be part of the underlying disease.

Convulsions (Seizures): Sertraline should be discontinued in any patient who develops seizures (See 'Special warnings and special precautions for use').

Musculoskeletal: Arthralgia, myalgia.

Hepatic/pancreatic: Rarely, pancreatitis and serious liver events (including hepatitis, jaundice and liver failure). Asymptomatic elevations in serum transaminases (SGOT and SGPT) have been reported in association with sertraline administration (0.8 – 1.3%), with an increased risk associated with the 200mg daily dose. The abnormalities usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Renal & urinary disorders: Urinary retention.

Reproductive: Hyperprolactinemia, galactorrhoea, menstrual irregularities, anorgasmy.

Skin and allergic reactions: Rash (including rare reports of erythema multiforme, photosensitivity), angioedema, ecchymoses, pruritus and anaphylactoid reactions.

Metabolic: Rare cases of hyponatremia have been reported and appeared to be reversible when sertraline was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients, and patients taking diuretics or other medications.

Haematologic: There have been rare reports of altered platelet function and/or abnormal clinical laboratory results in patients taking sertraline. While there have been reports of thrombocytopenia, abnormal bleeding or purpura in several patients taking sertraline, it is unclear whether sertraline had a causative role. See also 'Special warnings and special precautions for use'.

General Malaise.

Other: Withdrawal reactions have been reported with Sertraline. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with sertraline should be avoided. The majority of symptoms experienced on withdrawal of sertraline are non-serious and self-limiting.

Adverse events from paediatric clinical trials: In paediatric clinical trials in depression the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: dry mouth (2.1% vs 0.5%), hyperkinesia (2.6% vs 0.5%), tremor (2.1% vs 0%), diarrhoea (9.5% vs 1.6%) vomiting (4.2% vs 1.1%), agitation (6.3% vs 1.1%), anorexia (5.3% vs 1.1%) and urinary incontinence (2.1% vs 0%). Suicidal thoughts and suicide attempts were mainly observed in clinical trials with Major Depressive Disorder.

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).

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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
Neolab Limited
57 High Street
Odiham
Hants
RG29 1LF

8 MARKETING AUTHORISATION NUMBER(S)
PL 08137/0142

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/09/2007

10 DATE OF REVISION OF THE TEXT
24/09/2007

PATIENT INFORMATION LEAFLET
Sertraline 50 mg & 100 mg Tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

What is in your medicine?

The name of your medicine is Sertraline Tablets.

Each white tablet contains 50 mg or 100 mg of the active ingredient sertraline (as hydrochloride). The 50 mg tablets have a breakline and are marked with 'SRN 50' on one side and 'NEO' on the other side. The 100 mg tablets are marked with 'SRN 100' on one side and 'NEO' on the other side.

Other ingredients: Microcrystalline cellulose, maize starch, sodium starch glycolate (Type A), magnesium stearate, hypromellose, macrogol 6000 and titanium dioxide (E171).

Sertraline 50 mg & 100 mg Tablets are supplied in packs of 28 tablets.

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

The Marketing Authorisation Holder and manufacturer is Neolab Ltd., 57 High Street, Odiham, Hants, RG29 1LF.

Uses

Sertraline Tablets are used to treat the following conditions:
- The symptoms of depression (feelings of sadness, tearfulness, inability to sleep or enjoy life as you once used to) and any anxiety you may have at the same time.
- Obsessive-compulsive disorder (OCD). OCD is 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). PTSD can occur after a very emotionally traumatic experience. Some of the symptoms of PTSD are similar to depression and anxiety.

Low levels of a substance called serotonin in the brain are thought to be a cause of depression and these related disorders. SSRIs work by bringing the level of serotonin back up to normal.

Before taking your medicine

DO NOT take this medicine if:
- You have ever had an allergic reaction before (e.g., rash, itching, swollen face or lips, or shortness of breath) to sertraline or to any of the other ingredients listed above.
- 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, moclobemide, phenelzine, tranylcypromine and isocarboxazid.
- You have liver problems.
- You are a child under 6 years of age suffering from an obsessive compulsive disorder.
- You are a child or adolescent under 18 years of age suffering from depression.
- You are taking a medicine called pimozide (for the treatment of schizophrenia or psychosis).

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Tell your doctor immediately if the answer is YES to any of the following questions:
- Do you have epilepsy, or are you receiving ECT (electro-convulsive therapy) treatment?
- Do you have diabetes, as your insulin/medication dose may require adjusting?
- Do you have any kidney problems?

Sert/0141-0142/V2/March 2006

- Do you have any bleeding disorders?
- Are you pregnant, think you may be pregnant, or are thinking of becoming pregnant?
- Are you are breastfeeding or planning to start breastfeeding?

This medicine may make you feel drowsy or affect your concentration; you should not drive or operate machinery if affected. Alcohol should be avoided whilst taking this medication.

Tell your doctor or pharmacist if you are taking any other medicines, or have taken any recently. This includes medicines you have bought without a prescription e.g. aspirin or other pain killers known as NSAIDs (non-steroidal anti-inflammatory drugs).

This medicine may affect the way some other medicines work. These include lithium, tryptophan and diazepam (for depression, anxiety and other mental disorders) as well as tricyclic antidepressants (e.g. imipramine, desipramine, amitryptyline); tramadol (a painkiller); sumatriptan (for migraine); fenfluramine (an appetite suppressant); tolbutamide (for diabetes); cimetidine (an ulcer medicine); or warfarin (used to thin the blood). Only take other medicines if your doctor tells you to do so.

The herbal remedy St John's Wort (*Hypericum perforatum*) should not be taken at the same time as this medicine. If you already take St John's Wort, stop taking it and mention it to your doctor at your next visit.

If you have to go to another doctor or to hospital tell them that you are being treated with sertraline. The results of a blood/urine/other test can be affected by sertraline.

Taking your medicine

The tablets should be swallowed whole with a drink of water. Try to take the tablets at the same time each day, with or without a meal. Keep taking the tablets regularly each day.

The usual dose of Sertraline Tablets is 50 mg taken once a day. Doctors will sometimes prescribe a higher dose, up to a maximum of 200 mg daily. Your doctor should not make a change to your dose more than once a week.

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 the medication. For a small number of people, there may be an increase in suicidal thoughts and behaviour in the early stages of treatment with any antidepressant, including SSRIs. This is nothing to be ashamed of. If you have any distressing thoughts or experiences during these first few weeks, tell your doctor or go to the nearest hospital immediately.

Even when you feel better you should continue to take the 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.

What to do if you take an overdose?

Do not take more tablets than your doctor tells you to. If you have accidentally taken more than you should have, contact your doctor or go to your nearest hospital casualty department immediately.

What to do if you forget to take a dose?

If you have forgotten to take your medicine, just take your next dose at the usual time. Do not take a double dose to make up for the missed dose.

Possible Side-Effects

Any medicine can cause side effects in some people. For most people these side effects are not severe and they get better over time. The most common side effects of sertraline are nausea (feeling sick), stomach upsets, indigestion, dry mouth, loss of appetite, insomnia (difficulty sleeping), drowsiness, dizziness, increased sweating, headache and a sense of feeling tense or nervous. If such undesirable effects cause you discomfort or are long lasting, check with your doctor or pharmacist.

If any of the following occur, stop taking the tablets and tell your doctor immediately:

- Allergic reactions causing difficulties in breathing, swelling, rash or itching (especially affecting the whole body).

- Convulsions.

If you develop any of the following, tell your doctor as soon as possible:
- Fever, rigidity or muscle stiffness.
- A yellowing of your skin or whites of your eyes (jaundice).
- Psychological effects, such as confusion, agitation, anxiety, not being able to concentrate or or think properly, panic attacks, aggression, memory loss, hallucinations, loss of feeling of identity.
- Effects on the nervous system, such as tingling, numbness or uncontrollable twitching, jerking or writhing movements.
- Effects on the urinary and reproductive systems, such as difficulty passing urine, changes to sexual drive or function (e.g. not being able to experience orgasm), menstrual irregularities, increased production of breast milk or breast enlargement.
- Rapid heart beat and changes to blood pressure causing dizziness on standing up.
- Unexplained bruising or bleeding, skin rashes, itching and sensitivity to light.

Symptoms such as dizziness, tingling, headache, anxiety and feelings of sickness may occur if treatment with Sertraline Tablets is stopped too quickly (See 'Stopping treatment with Sertraline Tablets' below). Contact your doctor if you experience troublesome symptoms on stopping treatment.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Stopping treatment with Sertraline Tablets

Some patients experience withdrawal/discontinuation symptoms when they stop taking SSRIs. These can include headaches, feeling dizzy, shaky, sick, anxious, agitated or confused. Some people experience tingling sensations, pins and needles, burning sensations, electric-shock like sensations or find 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.

Storing your medicine

Do not take this medicine after the expiry date shown on the carton.

Keep all medicines out of the reach and sight of children. Your medicines can harm them. REMEMBER this medicine is for you. Only a doctor can prescribe it for you. Never give it to others – it may harm them even if their symptoms are the same as yours.

This information was prepared March 2006.

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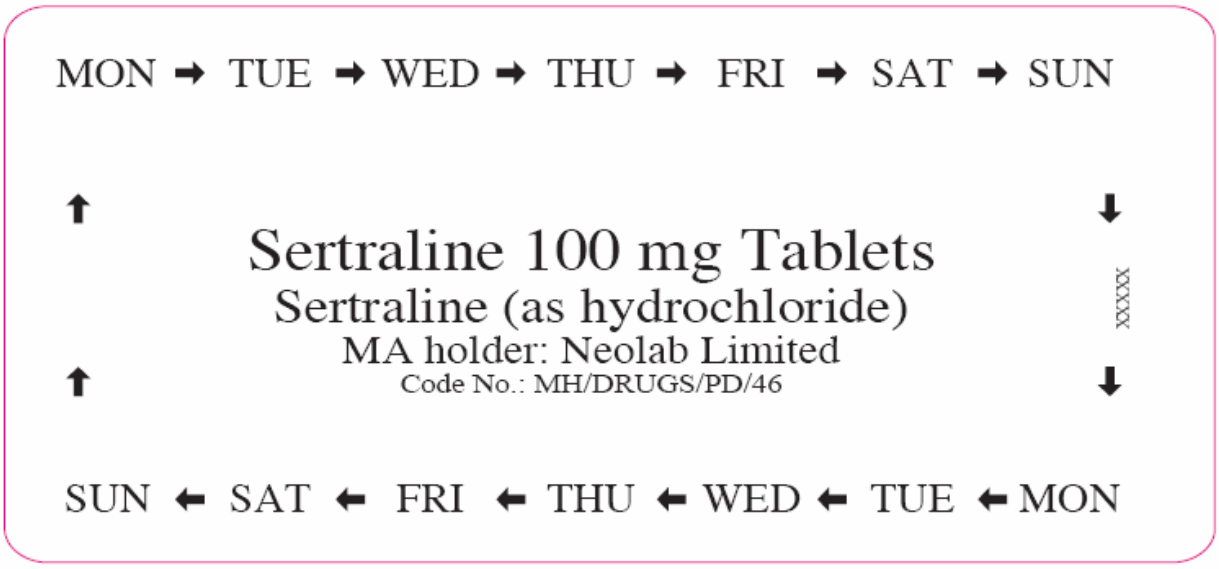
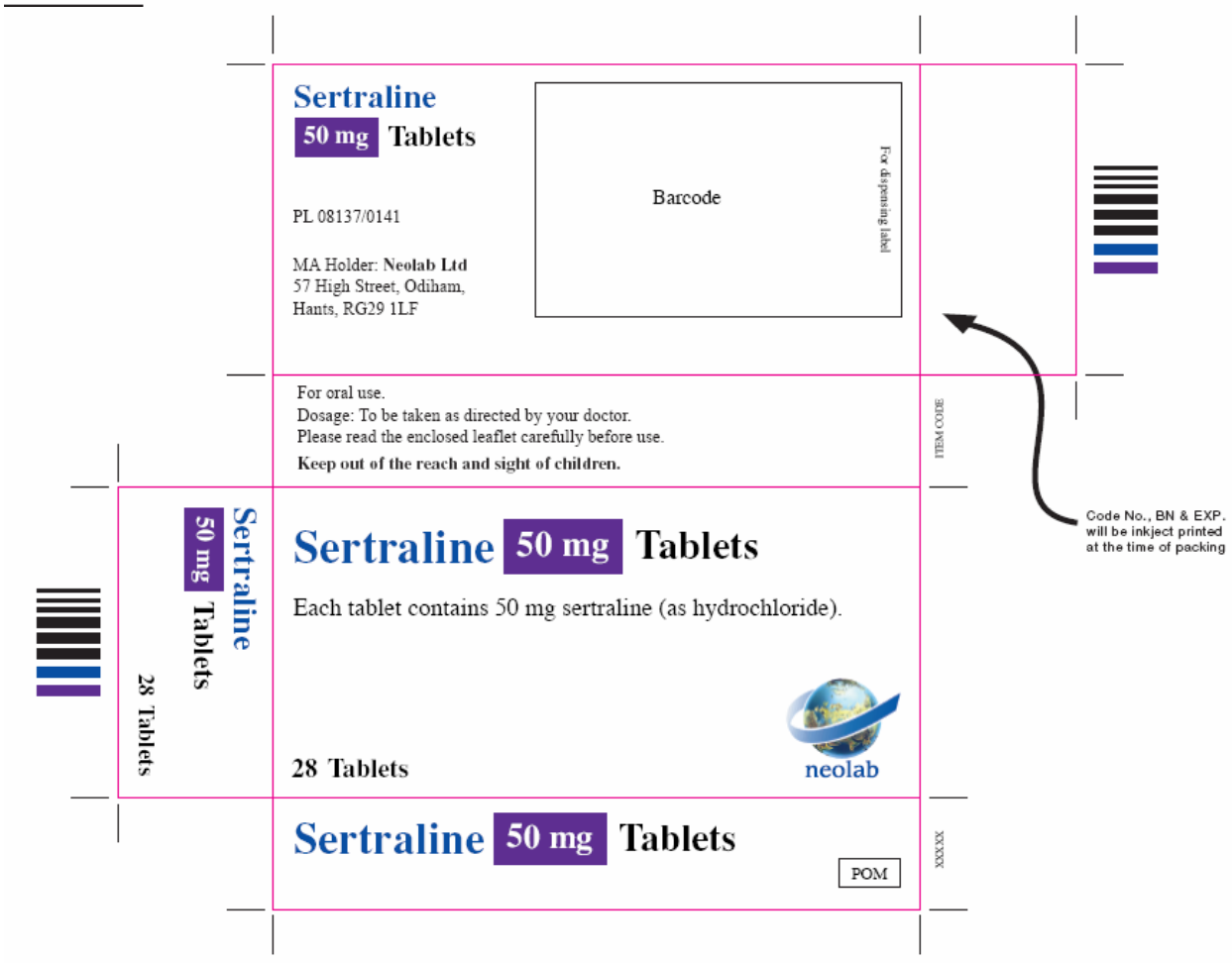

MON ➡ TUE ➡ WED ➡ THU ➡ FRI ➡ SAT ➡ SUN
Sertraline 100 mg Tablets
Sertraline (as hydrochloride)
MA holder: Neolab Limited
Code No.: MH/DRUGS/PD/46
XXXXX
SUN ⬅ SAT ⬅ FRI ⬅ THU ⬅ WED ⬅ TUE ⬅ MON


Sertraline
50 mg Tablets
PL 08137/0141
MA Holder: Neolab Ltd
57 High Street, Odiham,
Hants, RG29 1LF
Barcode
For dispensing label
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.
ITEM CODE
Code No., BN & EXP. will be inkject printed at the time of packing
Sertraline 50 mg Tablets
28 Tablets
Sertraline 50 mg Tablets
Each tablet contains 50 mg sertraline (as hydrochloride).
28 Tablets
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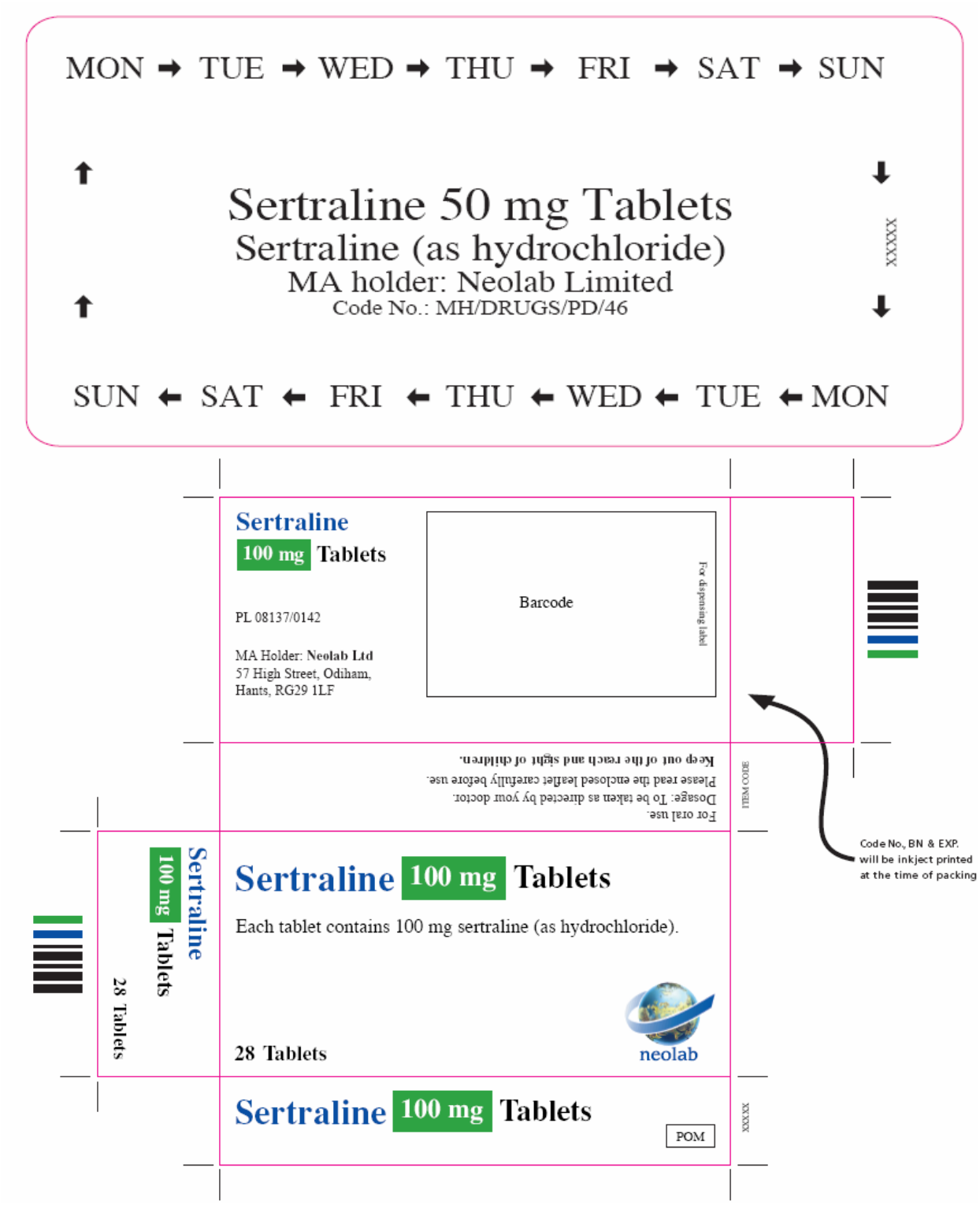
Sertraline 50 mg Tablets
POM
XXXXX


MON ➡ TUE ➡ WED ➡ THU ➡ FRI ➡ SAT ➡ SUN
Sertraline 50 mg Tablets
Sertraline (as hydrochloride)
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For dispensing label
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Sertraline 100 mg Tablets
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28 Tablets
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Sertraline 100 mg Tablets
POM
XXXX
Sertraline
100 mg Tablets
28 Tablets