



**SERTRALINE 50 MG AND 100 MG TABLETS**

**PL 20416/0201-2**

**UKPAR**

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## **SERTRALINE 50 MG AND 100 MG TABLETS**

**PL 20416/0201-2**

### **LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Crescent Pharma Limited Marketing Authorisations (licences) for the medicinal products Sertraline 50 mg and 100 mg Tablets (product licence numbers: 20416/0201 and 20416/0202). These tablets are available only with a prescription and are used to treat depression, obsessive compulsive disorder (OCD) or post traumatic stress disorder (PTSD) in adults. Sertraline is also used to treat OCD in children of 6 six years and older.

Sertraline 50 mg and 100 mg Tablets contain the active ingredient sertraline hydrochloride, which acts on nerve cells in the brain helping to control the behaviour associated with depression, OCD or PTSD.

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

# **SERTRALINE 50 MG AND 100 MG TABLETS**

**PL 20416/0201-2**

## **SCIENTIFIC DISCUSSION**

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## INTRODUCTION

The UK granted marketing authorisations for the medicinal products Sertraline 50 mg and 100 mg Tablets (PL 20416/0201-2) to Crescent Pharma Limited on 6 July 2007. These products are prescription only medicines (POM).

These applications were submitted as generic applications according to Article 10.1 of EC Directive 2001/83. The cross reference products are Lustral 50 mg and 100 mg tablets (PL00057/0308-9), licensed to Pfizer Ltd on 19 November 1990.

These standard and complex national abridged applications are for tablets containing 50 mg and 100 mg of the selective serotonin re-uptake inhibitor drug (SSRI), sertraline. As the cross-reference products were granted prior to the introduction of current legislation, no Public Assessment Reports (PARs) were generated for them.



The applicant certifies that no materials of animal or human origin are contained in, or used in the manufacturing process for, the proposed product. Declarations have been provided from the suppliers regarding TSE.

### **Manufacture**

A description and flow-chart of the manufacturing method has been provided. Manufacturing sites have been inspected by the relevant authorities and were found to be satisfactory.

Satisfactory in process controls are carried out during the manufacturing process. Process validation has been carried out on batches of each tablet strength. The results are satisfactory.

### **Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification.

### **Reference standards or materials**

A sertraline hydrochloride working standard reference was used in the analysis of the sertraline tablets. A satisfactory certificate of analysis for the mentioned working standard has been provided.

### **Container-closure system**

Sertraline 50 and 100 mg tablets will be marketed in blister packs of 14. The blisters are white opaque PVC, coated with PVdC or white opaque PVC as the forming material and pre-printed aluminium foil as the lidding foil. Two or four strips of such blisters will be packed in a pre-printed carton to give a marketed pack of 28 or 56 tablets. All the components of the primary packaging are food grade materials and comply with European Pharmacopoeia requirements. All primary product packaging complies with EU legislation regarding contact with food. Satisfactory in-house specifications and suppliers' Certificates of Conformance for these blister laminates and the aluminium foil lidding material have been provided.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. No special storage conditions are needed.

### **Bioequivalence/bioavailability**

The applicant has only studied the bioequivalence of the 100mg presentation. A satisfactory justification has been provided for an exemption from the need to study the 50mg presentation.

### **Conclusions**

Marketing Authorisations for Sertraline 50 mg and 100 mg Tablets may be granted.

## **PRECLINICAL ASSESSMENT**

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

## CLINICAL ASSESSMENT

### Background

Sertraline is a selective serotonin re-uptake inhibitor drug (SSRI) that is well characterised in the literature.

### Indications

The indications listed in the submitted Summary of Product Characteristics (SPC) are in line with those of the reference product and are satisfactory.

### Dose and dose schedule

The recommended dose and dose schedule given in the submitted SPC are satisfactory for products of this nature.

### Toxicology

No new data are submitted and none are required for these types of applications.

### Pharmacodynamics

No new data are submitted. The pharmacodynamics of sertraline are well described and published data are presented and reviewed in some detail by the applicant. It 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.

### Pharmacokinetics

No new data are submitted. The pharmacokinetics of sertraline are well described. It exhibits dose proportional pharmacokinetics over a range of 50–200 mg. After oral administration, peak blood levels occur at about 4.5 - 8.4 hours. Sertraline has a plasma half-life of approximately 26 hours. The principal metabolite, N-desmethylsertraline, is inactive in *in vivo* models of depression. Sertraline and N-desmethylsertraline are both extensively metabolised and only a small amount (<0.2 %) is excreted unchanged in urine.

### Bioequivalence

A bioequivalence study was carried out, comparing the 100 mg strength with the UK reference product, Lustral 100mg tablets, manufactured by Pfizer. The study was carried out in compliance with Good Clinical Practice and the applicant has justified the use of only the 100 mg tablet strength in the bioequivalence study. Bioequivalence has been satisfactorily demonstrated in accordance with CPMP criteria.

### Efficacy

No new data are submitted and none are required for these types of applications. Efficacy is reviewed in the Clinical Expert Report. The reference product is established and the applications depend upon the ability to show bioequivalence with the reference product.

### Safety

No new data are submitted and none are required for these types of applications. There were no important adverse events in the bioequivalence study and the literature review in the expert report identifies no new safety issues.



**Expert reports**

An appropriately qualified consultant in pharmaceutical medicine provides the expert report. It consists of a well referenced review of the published literature relating to the pharmacology, efficacy and safety of sertraline and a critical appraisal of the bioequivalence study, including a justification that a further bioequivalence study is not required for the 50mg tablet strength.

**Discussion**

The requested indications are acceptable.

Bioequivalence has been satisfactorily demonstrated in accordance with CPMP criteria for both the 50 mg and 100 mg tablet strengths.

**Medical conclusion**

Marketing authorisations may be granted for these preparations.

## **OVERALL CONCLUSION AND RISK BENEFIT 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.

### **PRECLINICAL**

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

No new or unexpected safety concerns arise from these applications.

### **EFFICACY**

The efficacy of sertraline has been well documented in the past. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the cross-reference products.

### **RISK BENEFIT ASSESSMENT**

The quality of these products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products. The risk benefit ratio is considered to be positive.

## SERTRALINE 50 MG AND 100 MG TABLETS

PL 20416/0201-2

### STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 9 May 2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 30 August 2005
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 10 January 2006
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 7 April 2006
5	Following assessment of the response the MHRA requested further information relating to the quality dossier on 5 June 2006
6	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 16 June 2006
7	Following assessment of the response the MHRA requested further information relating to the quality dossier on 16 June 2006
8	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 17 July 2006
9	Following assessment of the response the MHRA requested further information relating to the clinical dossier on 28 November 2006
10	The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 19 January 2007
11	The application was determined on 6 July 2007

## SUMMARY OF PRODUCT CHARACTERISTICS

### 50 mg strength:

#### 1 NAME OF THE MEDICINAL PRODUCT

Sertraline 50 mg film-coated Tablets

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Sertraline hydrochloride equivalent to 50 mg sertraline.  
For excipients, see 6.1.

#### 3 PHARMACEUTICAL FORM

Film-coated tablets

White capsule shaped, film-coated tablets debossed with 'A' on one side and '81' with a scoreline on the other.

#### 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 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*

Sertraline tablets 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 50mg daily and the usual antidepressant dose is 50mg daily. In some patients, doses higher than 50mg may be required.

**Obsessive Compulsive Disorder** The starting dose is 50mg daily, and the therapeutic dose range is 50-200mg 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 50mg daily may be required. In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50mg increments over a period of weeks to a maximum of 200mg daily. Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level. Dosage during prolonged maintenance therapy should be kept at the lowest effective level, with subsequent adjustments depending on therapeutic response. The onset of therapeutic effect may be seen within 7 days, although 2-4 weeks (and even longer in OCD) are usually necessary for full activity. A longer treatment period, even beyond 12 weeks in some cases, may be required in the case of a therapeutic trial in PTSD.

**Use in children aged 6-17 years:** Treatment should only be *initiated* by specialists. The safety and efficacy of Sertraline has been established in paediatric OCD patients (aged 6-17). The administration of Sertraline to paediatric OCD patients (aged 13-17) should commence at 50 mg/day. Therapy for paediatric OCD patients (aged 6-12) should commence at 25 mg/day increasing to 50 mg/day after 1 week. Subsequent doses may be increased in case of lack of response in 50 mg/day increments up to 200mg/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 are reported to be similar to that in younger patients.

Sertraline tablets are for oral administration only.

#### **4.3 *Contraindications***

Sertraline tablets are 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 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 - Interaction with Other Medicaments 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 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.

**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 reported to be 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.

**Diabetes** : In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may be needed to be adjusted.

**Seizures** : Seizures are a potential risk with antidepressant or antiobsessional drugs. The drug should be discontinued in any patient who develops seizures. Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued if there is an increase in seizure frequency.

**Electroconvulsive therapy (ECT) :** Since there is little clinical experience of concurrent administration of Sertraline and ECT, caution is advisable.

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

**Suicide :** As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved and it is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

**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 drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders.

#### 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 use of pimozide and sertraline is contra-indicated.

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

**Lithium and Tryptophan :** Co-administration of Sertraline and lithium did not significantly alter lithium pharmacokinetics in placebo-controlled trials in normal volunteers. However, co-administration of Sertraline with lithium resulted 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.*

**Warfarin** : Co-administration of sertraline (200mg daily) with warfarin may result 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.

**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 (200mg 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.**

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 tablets 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 and tremor. Most were of mild to moderate severity.

The following adverse reactions of sertraline have been reported :

**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.

**Others**: 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**

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**

Pharmacotherapeutic classification: antidepressants; selective serotonin reuptake inhibitors

ATC code: N06A B06

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 reported 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 50 mg/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. 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 to younger adults. 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.

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***

#### ***Core:***

Calcium hydrogen phosphate

Microcrystalline cellulose

Hydroxypropylcellulose

Sodium starch glycolate

Magnesium stearate

#### ***Film coat:***

Titanium dioxide (E171)

Hypromellose

Macrogol 400

Polysorbate 80

### **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***

White opaque PVC/ Aluminium blister strips in a carton (Packs of 28 or 56)

White opaque PVdC coated PVC/ Aluminium blister strips in a carton (Packs of 28 or 56)

Not all packs sizes may be marketed

### **6.6 *Special precautions for disposal***

No special requirements.

- 7      MARKETING AUTHORISATION HOLDER**  
Crescent Pharma Limited  
Units 3 and 4, Quidhampton Business units  
Polhampton Lane  
Overton  
Hampshire RG25 3ED, UK
- 8      MARKETING AUTHORISATION NUMBER(S)**  
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06/07/2007
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**100mg strength:**

- 1      NAME OF THE MEDICINAL PRODUCT**  
Sertraline 100 mg film-coated Tablets
- 2      QUALITATIVE AND QUANTITATIVE COMPOSITION**  
Each tablet contains Sertraline hydrochloride equivalent to 100 mg sertraline.  
For excipients, see 6.1.
- 3      PHARMACEUTICAL FORM**  
Film-coated tablets  
White capsule shaped, film-coated tablets debossed with ‘A’ on one side and ‘82’  
with a scoreline on the other.
- 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 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*

**Sertraline tablets 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 50mg daily and the usual antidepressant dose is 50mg daily. In some patients, doses higher than 50mg may be required.

*Obsessive Compulsive Disorder* The starting dose is 50mg daily, and the therapeutic dose range is 50-200mg 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 50mg daily may be required. In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50mg increments over a period of weeks to a maximum of 200mg daily. Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level. Dosage during prolonged maintenance therapy should be kept at the lowest effective level, with subsequent adjustments depending on therapeutic response. The onset of therapeutic effect may be seen within 7 days, although 2-4 weeks (and even longer in OCD) are usually necessary for full activity. A longer treatment period, even beyond 12 weeks in some cases, may be required in the case of a therapeutic trial in PTSD.

**Use in children aged 6-17 years:** Treatment should only be *initiated* by specialists. The safety and efficacy of Sertraline has been established in paediatric OCD patients (aged 6-17). The administration of Sertraline to paediatric OCD patients (aged 13-17) should commence at 50 mg/day. Therapy for paediatric OCD patients (aged 6-12) should commence at 25 mg/day increasing to 50 mg/day after 1 week. Subsequent doses may be increased in case of lack of response in 50 mg/day increments up to 200mg/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 are reported to be similar to that in younger patients.

Sertraline tablets are for oral administration only.

#### 4.3 **Contraindications**

Sertraline tablets are 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 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 - Interaction with Other Medicaments 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 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.

**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 reported to be 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.

**Diabetes :** In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may be needed to be adjusted.

**Seizures :** Seizures are a potential risk with antidepressant or antiobsessional drugs. The drug should be discontinued in any patient who develops seizures. Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued if there is an increase in seizure frequency.

**Electroconvulsive therapy (ECT) :** Since there is little clinical experience of concurrent administration of Sertraline and ECT, caution is advisable.

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

**Suicide :** As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved and it is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

**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 drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders.

#### 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 tablets (200mg daily) for 9 days, no adverse effect on cognitive or psychomotor performance relative to

placebo, following a single dose of 500mg/kg alcohol has been reported. However, the concomitant use of Sertraline and alcohol in depressed patients is not recommended.

**Lithium and Tryptophan :** Co-administration of Sertraline and lithium did not significantly alter lithium pharmacokinetics in placebo-controlled trials in normal volunteers. However, co-administration of Sertraline with lithium resulted 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.*

**Warfarin :** Co-administration of sertraline (200mg daily) with warfarin may result 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.

**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 (200mg 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.**

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 and tremor. Most were of mild to moderate severity.

The following adverse reactions of sertraline have been reported :

**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.

**Others**: 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**

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**

Pharmacotherapeutic classification: antidepressants; selective serotonin reuptake inhibitors

ATC code: N06A B06

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 reported 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 50 mg/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. 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 to younger adults. 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.

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***

#### ***Core:***

Calcium hydrogen phosphate

Microcrystalline cellulose

Hydroxypropylcellulose

Sodium starch glycolate

Magnesium stearate

#### ***Film coat:***

Titanium dioxide (E171)

Hypromellose

Macrogol 400

Polysorbate 80

### **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**

White opaque PVC/ Aluminium blister strips in a carton (Packs of 28 or 56)

White opaque PVdC coated PVC/ Aluminium blister strips in a carton (Packs of 28 or 56)

Not all packs sizes may be marketed

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Crescent Pharma Limited

Units 3 and 4, Quidhampton Business units

Polhampton Lane

Overton

Hampshire

RG25 3ED

UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20416/0202

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

06/07/2007

**10 DATE OF REVISION OF THE TEXT**

06/07/2007

# PATIENT INFORMATION LEAFLET

## PATIENT INFORMATION LEAFLET

P0133

## SERTRALINE 50mg and 100mg Film-Coated Tablets

**Please read this leaflet before you start taking this medicine and in addition, follow the advice given to you by your doctor. Keep this leaflet; you may want to read it again.**

If you have further questions please ask your doctor or 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.

The name of this medicine is Sertraline Film-Coated Tablets. The active ingredient is Sertraline.

In this leaflet:

- 1) What are Sertraline tablets and what are they used for?
- 2) Before you take Sertraline tablets
- 3) How to take Sertraline tablets
- 4) Possible side effects
- 5) Storing Sertraline tablets
- 6) Further information

The product licence holder and manufacturer of this medicine is Crescent Pharma Limited, Polhampton Lane, Overton, Hants RG25 3ED.

### 1. What are Sertraline Tablets and what are they used for?

Sertraline tablets contain Sertraline hydrochloride equivalent to 50 or 100mg Sertraline.

The other ingredients in the tablets are microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, calcium hydrogen phosphate, magnesium stearate, hypromellose, macrogol 400, polysorbate 80 and titanium dioxide (E171).

Sertraline tablets are white, film-coated and capsule shaped. The 50mg tablet is marked with an 'A' on one side and '81' with a scoreline on the other. The 100mg tablet is marked with an 'A' on one side and '82' on the other.

Sertraline tablets are available in packs of 28 or 56 tablets. (Not all pack sizes may be marketed.)

Sertraline belongs to a group of antidepressant drugs called Selective Serotonin Reuptake Inhibitors. It is used to treat depression, Obsessive Compulsive Disorder (OCD) or Post Traumatic Stress Disorder (PTSD) in adults. It is also used to treat OCD in children 6 years of age and over.

These tablets are not sleeping tablets or tranquilizers. They are not for anyone under the age of 18 years with depression, nor are they for children under 6 years with OCD. Treatment of children with Sertraline should only be initiated by specialists.

Depression is a clinical illness. If you have been feeling sad, tearful, unable to sleep properly or to enjoy life as you used to, Sertraline tablets may help. If you are not sure why you are on these tablets, ask your doctor.

### 2. Before you take Sertraline Tablets

Do not take Sertraline tablets if you:

- have had an allergic reaction to sertraline or any of the other ingredients
- have liver problems
- are taking, or have taken in the last two weeks, any medicines called monoamine oxidase inhibitors (MAOIs for short)
- are taking a medicine called pimozone

Consult your doctor immediately if you:

- are pregnant or think you might be pregnant
- are breast feeding
- have liver or kidney problems
- have diabetes or have had epileptic fits
- are being treated with electroconvulsive therapy (ECT)
- are being treated with any other medication for your illness, e.g. lithium, or another antidepressant or anti-obsessional drug
- are taking warfarin, tryptophan, sumatriptan, fenfluramine, diazepam, tolbutamide, cimetidine, tramadol, aspirin or other pain killers known as NSAIDs (Non-Steroidal Anti-inflammatory Drugs)
- have a history of bleeding disorders

Sertraline is not suitable for children under 6 years of age. Sertraline does not appear to be effective to treat depression in children or adolescents under 18 years of age and is not suitable for this use.

Your doctor may want you to have blood tests if you are taking lithium or warfarin.

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

Thoughts of suicide or self-harm can be part of depressive illness and they may increase after starting treatment with sertraline before the full benefit of treatment is seen. Tell your doctor immediately if you feel suicidal or have any distressing thoughts or experiences.

This medicine may cause drowsiness especially if you are taking it with other medicines, and may impair the abilities required to perform potentially hazardous tasks such as driving a car or operating machinery. Discuss the necessary precautions with your doctor if you wish to drive or use machinery while taking this medicine.

It is recommended that you avoid drinking alcohol when taking this medicine.

### **3. How to take Sertraline Tablets**

Swallow your tablets whole with a drink of water. It is best to take them at the same time each day, with or without a meal. Do not crush or chew your tablets.

The dose of Sertraline will depend on the nature of your illness and on how you respond to this medicine. The usual starting dose is 25mg or 50mg once a day. Thereafter the usual dose is 50mg once a day but higher doses may be needed, up to a maximum dose of 200mg daily. The label on the pack will tell you what dose to take. If you are still not sure, ask your doctor or pharmacist.

You may need to take Sertraline tablets for at least 2 to 4 weeks before you start to feel better. Your doctor will want to monitor your progress closely during this period. You must therefore keep taking Sertraline tablets to help you get better.

Your doctor should not change your dose more than once a week.

If you forget to take a tablet, do not take the missed tablet. Just take the next tablet at the right time. Do not double the dose.

Too many tablets taken at once can be dangerous. If you take too many tablets tell your doctor. If you are unable to contact your doctor go to your local hospital casualty department at once. Take the container with you so that the medicine can be identified.

### **4. Possible side effects**

Like all medicines, Sertraline tablets can have side effects, including dry mouth, feeling or being sick, loss of appetite, upset stomach, diarrhoea, abdominal pain, indigestion, shaky feeling (tremor), sweating, dizziness, change in sex drive or function (delay in ejaculation, inability to experience orgasm) and not being able to sleep or excessive sleepiness.

If you find any undesirable effects particularly troublesome or if they do not settle down with continued treatment, check with your doctor or pharmacist.

Other effects include:

- Effects on the nervous system, such as headache, tingling, numbness or uncontrollable twitching, jerking or writhing movements (these are more likely if you already experience such effects).
- Convulsions. You should tell your doctor immediately if you experience convulsions.
- Psychological effects, such as confusion, amnesia, agitation, aggression, mania/hypomania, hallucination, nervousness, panic reaction, reduced ability to react normally to everyday situations, loss of feeling of identity and effects associated with depression: anxiety and crying, increased suicidal thoughts or suicide attempt.
- Cardiovascular effects, including rapid heart beat and changes to blood pressure, including low blood pressure/dizziness on standing.
- Urinary and reproductive effects, such as not being able to pass water, menstrual irregularities and hormonal changes which could lead to abnormal production of breast milk or breast enlargement.
- Effects on the skin, including bruising easily, skin rash, itching and sensitivity to sunlight.

Other effects include the following: fever, rigidity, abnormal vision, feeling unwell, tiredness, joint or muscle pain as well as abnormalities in liver function tests, and rarely jaundice, inflammation of the pancreas or liver, or liver failure. Also abnormal bleeding and lower sodium content of the blood. Abnormal blood tests have been reported rarely.

Symptoms such as dizziness, tingling, headache, anxiety and nausea may occur if the treatment is stopped too quickly. These symptoms are generally non-serious and disappear within a few days. If you experience symptoms on stopping treatment, contact your doctor.

All medicines can cause allergic reactions. Serious allergic reactions are very rare. Any sudden wheeziness, difficulty in breathing, swelling, rash or itching (especially affecting the whole body) should be reported to a doctor immediately.

Tell your doctor straight away if you get any of these effects, or any other discomfort you do not understand.

### **5. Storing Sertraline Tablets**

#### **KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.**

This medicinal product does not require any special storage conditions. Unless your doctor tells you to, do not keep any tablets that you no longer need. Give them back to the pharmacist.

Do not take the tablets if the expiry date on the pack has passed.

### **6. Further information**

This leaflet does not contain all the information about this medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

If they are unable to help, you can contact the product licence holder whose address is given above.

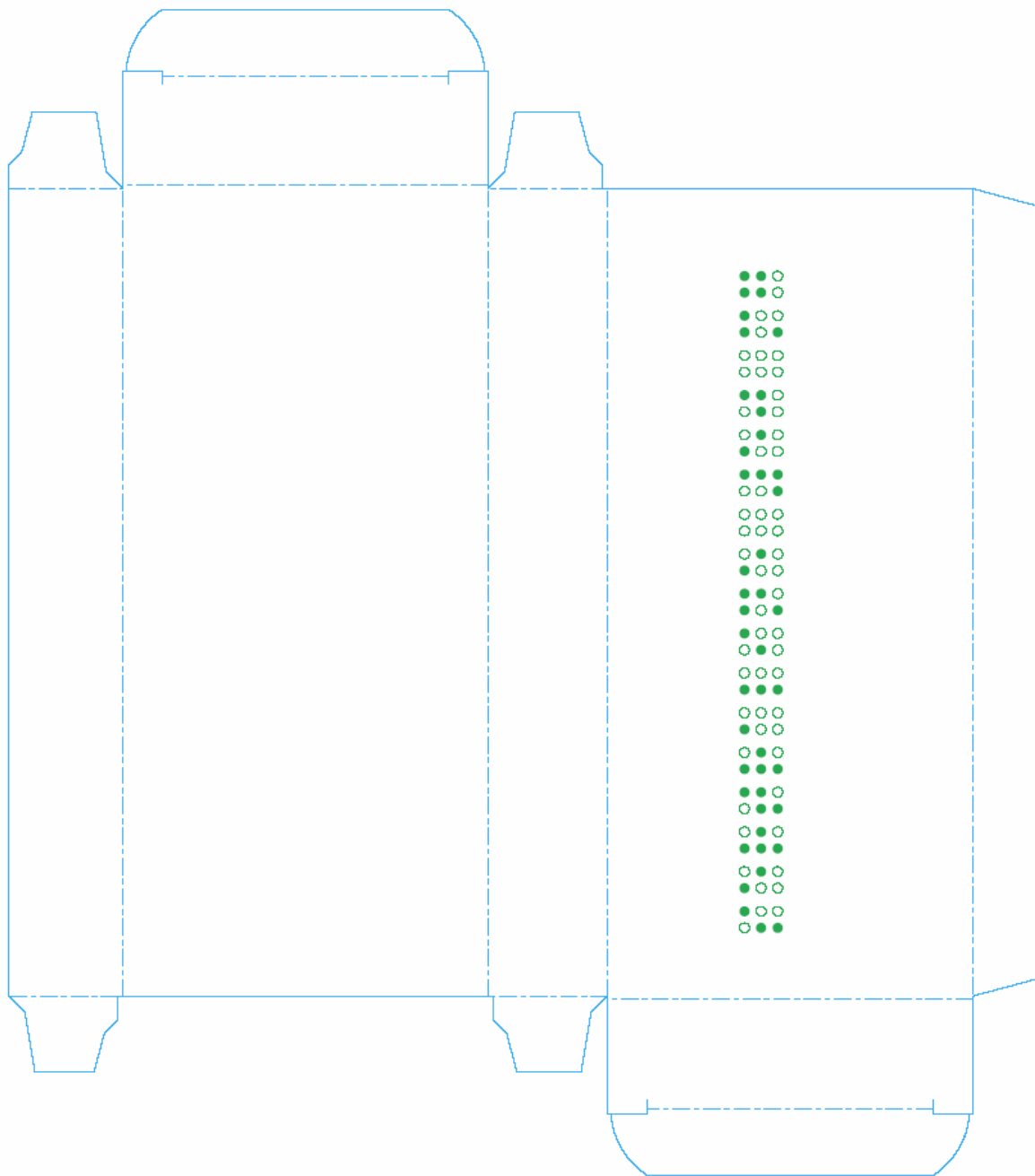
Date of revision of leaflet: January 2007

## LABELLING

**50 mg strength**

**Carton:**









SERTRALINE 50mg

**BOM**  
56  
Tablets

SERTRALINE 50mg  
56  
Film-coated tablets

Product License holder:  
Crescent Pharma Limited,  
Overton, Hants RG25 3ED  
PL 20416/0201

POSITION OF  
BARCODE



SERTRALINE 50mg film-coated tablets

For oral administration.  
Use as directed by the physician. Read the enclosed Patient Information Leaflet before use.  
**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.**  
Store in the original package.

SERTRALINE 50mg  
56  
Tablets



SERTRALINE  
50mg film-coated tablets

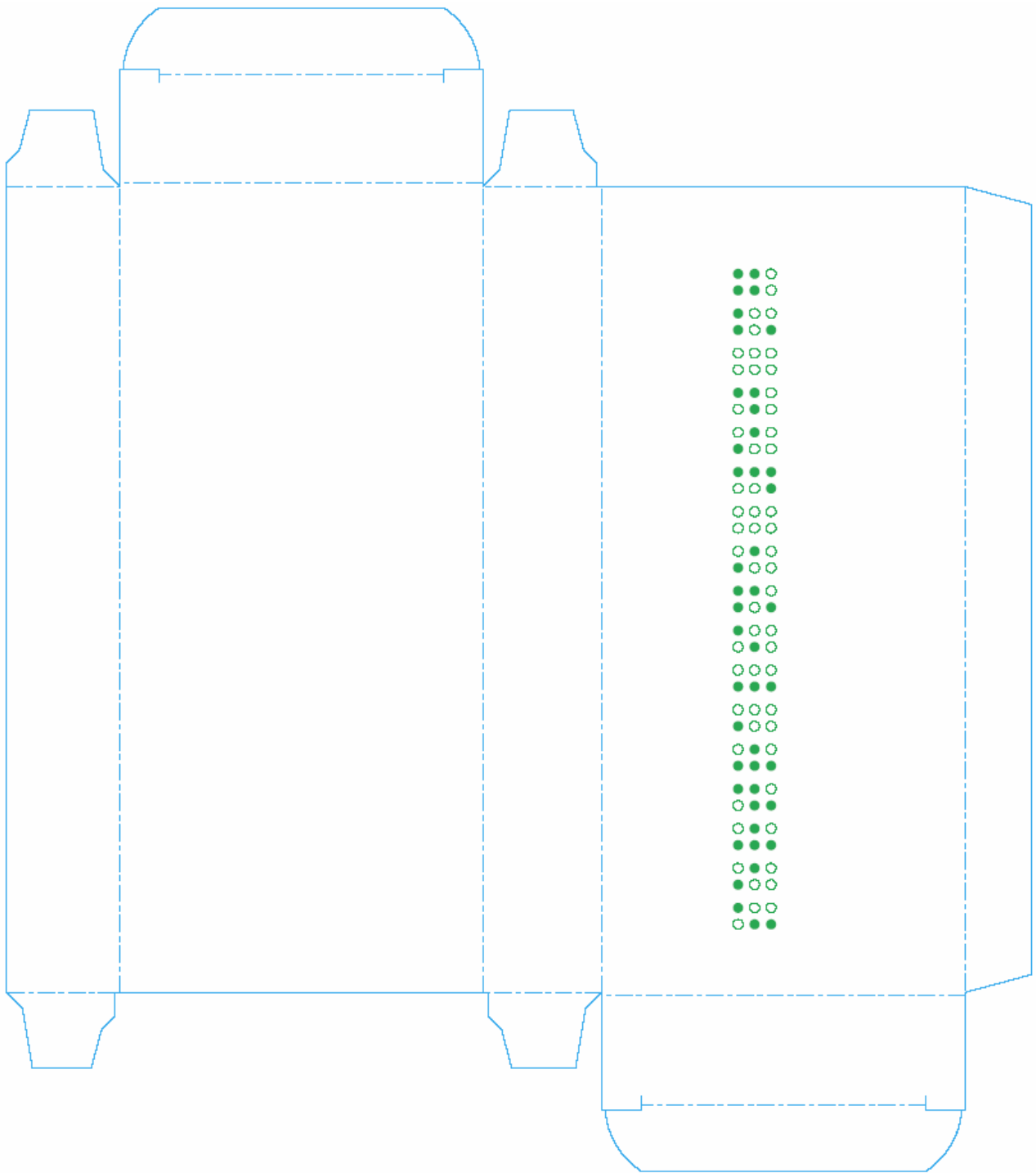
Each film-coated tablet contains:  
Sertraline Hydrochloride equivalent to 50mg Sertraline.

56  
Tablets

Batch No:  
Exp date:

56  
Tablets

xxxx



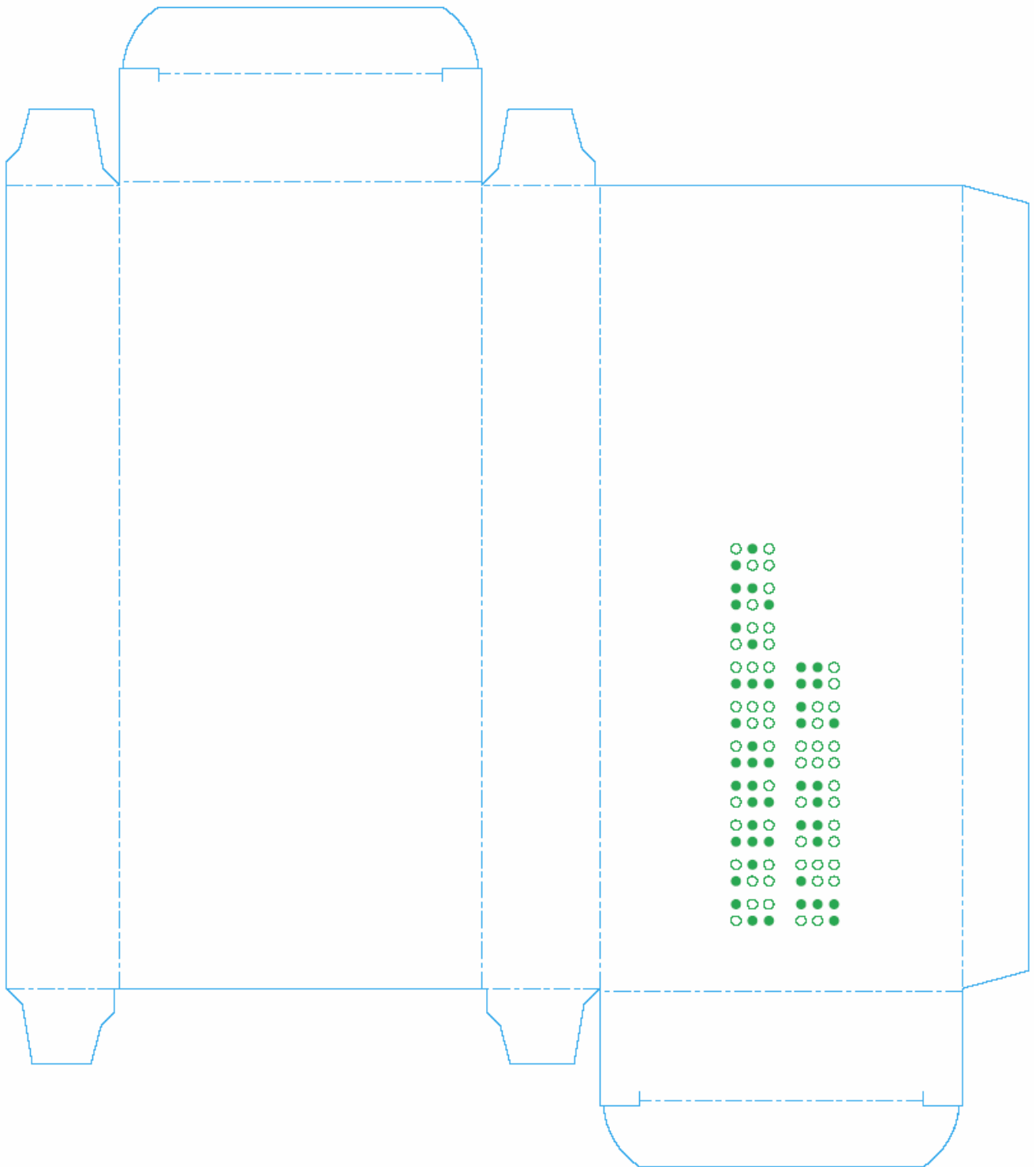
**Foil:**



100 mg strength

Carton:







SERTRALINE 100mg film-coated tablets 56 Tablets

SERTRALINE 100mg

56 Tablets

POM

Product License holder:  
Crescent Pharma Limited,  
Oventon, Hants RG26 3ED  
PL 2041 80202

POSITION OF  
BARCODE



SERTRALINE 100mg film-coated tablets

For oral administration.  
Use as directed by the physician. Read the enclosed Patient Information Leaflet before use.  
**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.**  
Store in the original package.

56 Tablets

SERTRALINE 100mg



SERTRALINE  
100mg film-coated tablets

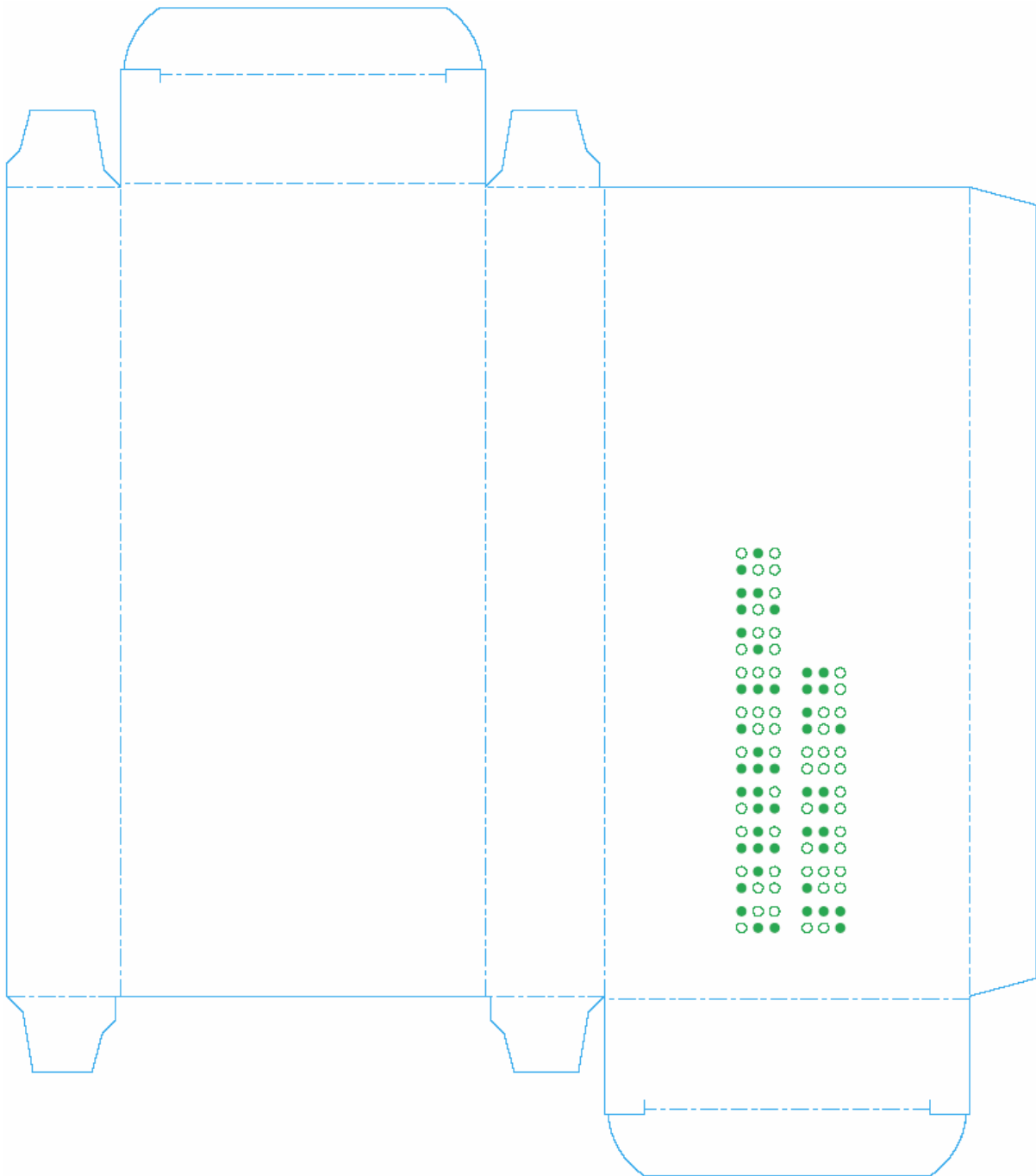
Each film-coated tablet contains:  
Sertraline Hydrochloride equivalent to 100mg Sertraline.

56 Tablets

Batch No:  
Exp date:

56 Tablets

xxx



**Foil:**

