

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sertraline 50mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg of sertraline, as sertraline hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, capsule shaped, biconvex, film coated tablets embossed with “50” on one side and “SET” on the other side with a bisect line separating “S” from “ET”.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sertraline is indicated for the treatment of:

Major depressive episodes. Prevention of recurrence of major depressive episodes.

Panic disorder, with or without agoraphobia.

Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years.

Social anxiety disorder.

Post traumatic stress disorder (PTSD)

4.2 Posology and method of administration

Sertraline should be given as a single daily dose. Sertraline can be administered with or without food.

The tablets may be broken along the bisect line for reasons of dosing (see *Post-Traumatic Stress Disorder & Use in children aged 6-17 years with OCD*)

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 25mg/day. After one week, the dose should be increased to 50mg 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should be reviewed periodically by the prescribing physician to determine response to therapy and treatment should be withdrawn if there is no clear evidence of efficacy.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 with OCD

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 25mg/day increasing to 50mg/day after 1 week. Subsequent doses may be increased in case of lack of response in 50mg/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 50mg, 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.

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.

Sertraline tablets are for oral administration only.

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 - Interaction with Other Medicaments and Other Forms of Interaction).

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.

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 film-coated Tablets should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline film-coated Tablets 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 film-coated Tablets and ECT, caution is advisable.

Mania Sertraline film-coated Tablets should be used with caution in patients with a history of mania/hypomania. Sertraline film-coated Tablets should be discontinued in any patient entering a manic phase.

Suicide / Suicidal thoughts or clinical worsening

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

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

Patients with a history of suicide-related events or those exhibiting significant degree of suicidal ideation prior to the commencement of treatment are known to be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared with placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviours and to seek medical advice immediately if these symptoms present.

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.

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 and adolescents under 18 years of age 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.

Sertraline film-coated Tablets should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with OCD. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

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 film-coated Tablets are 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 (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 film-coated Tablets and alcohol in depressed patients is not recommended.

Lithium and Tryptophan In placebo-controlled trials in normal volunteers, the co-administration of Sertraline film-coated Tablets and lithium did not significantly alter lithium pharmacokinetics.

Co-administration of Sertraline film-coated Tablets 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 film-coated Tablets. 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 for 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.

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 Fertility, 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.

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

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 film-coated Tablets is considered necessary, discontinuation of breast feeding should be considered.

Fertility Animal data did not show an effect of sertraline on fertility parameters (see section 5.3.).

Human case reports with some SSRIs have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

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.

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

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

Sertraline has been evaluated in paediatric MDD patients aged 6 – 17 years in two 10 week placebo controlled studies (n=364) and one 24 week open label study. Evidence of efficacy was not adequately demonstrated in the individual studies, however, there was evidence of efficacy in a planned combined study analysis.

The following adverse events were observed in clinical trials in children and adolescents (aged 6 –17 years old) with major depressive disorder and occurred at a frequency of at least 2% and at least twice that of placebo: Anorexia (5.3% vs 1.1%), Dry mouth (2.1% vs 0.5%), Hyperkinesia (2.6% vs 0.5%), Tremor (2.1% vs 0%), Urinary Incontinence (2.1% vs 0%), Diarrhoea (9.5% vs 1.6%), Vomiting (4.2% vs 1.1%) and Agitation (6.3% vs 1.1%). In the trials there were a total of 17 discontinuations due to adverse events (9%) from sertraline and 4 (2.1%) from placebo. The most common reasons for discontinuation, due to adverse events, whether or not related to sertraline, were aggressive reaction (1.6%), agitation (1.6%) and suicidal ideation (1.6%), hyperkinesias (1.1%), suicide attempt (1.1%) and aggravated depression (1.1%).

In the safety analysis, events of suicide attempt were reported in the same number of patients in sertraline (2/189, 1.1%) and placebo (2/184, 1.1%) with an incidence of suicide attempts in sertraline-treated subjects of 1.1% (2 attempts in 2/189 subjects) versus 1.6% in placebo-treated subjects (3 attempts in 2/184 subjects). Suicidal ideation was reported by 3 sertraline treated patients (1.6%) and no placebo treated patients. No causal relationship to sertraline has been established, however, owing to the inherent risk of suicide attempt in patients with MDD, it is recommended to be attentive to the occurrence of suicidal thoughts.

4.9 Overdose

On the available evidence, 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 group: Selective serotonin reuptake inhibitors (SSRI),
ATC code: N06 AB06

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

Sertraline has not demonstrated potential for abuse. In a placebo-controlled, double-blind randomized study of the comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria and abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforcer in rhesus monkeys trained to self administer

cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

Clinical Trials

Major Depressive Disorder

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

Post traumatic stress disorder (PTSD)

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

Paediatric OCD

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

endpoint, were 53% of sertraline-treated patients compared to 37% of placebo-treated patients ($p=0.03$).

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

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

Sertraline undergoes extensive first-pass hepatic metabolism.

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

Elimination

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

Pharmacokinetics in specific patient groups

Paediatric patients with OCD

Pharmacokinetics of sertraline was studied in 29 paediatric patients aged 6-12 years old, and 32 adolescent patients aged 13-17 years old. Patients were gradually uptitrated to a 200 mg daily dose within 32 days, either with 25 mg starting dose and increment steps, or with 50 mg starting dose or increments.

The 25 mg regimen and the 50 mg regimen were equally tolerated. In steady state for the 200 mg dose, the sertraline plasma levels in the 6-12 year old group were approximately 35% higher compared to the 13-17 year old group, and 21% higher compared to adult reference group. There was no significant difference between boys and girls regarding clearance. A low starting dose and titration steps of 25 mg are therefore recommended for children, especially with low bodyweight. Adolescents could be dosed like adults.

Adolescents and elderly

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

Liver function impairment

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

Renal impairment

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

Pharmacogenomics

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

5.3 Preclinical safety data

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, Microcrystalline Ph Eur (E460)
Calcium Hydrogen Phosphate Dihydrate Ph Eur
Silica, Colloidal Anhydrous Ph Eur
Sodium Starch Glycolate (Type-A) Ph Eur
Hydroxypropyl cellulose Ph Eur (E463)
Magnesium Stearate Ph Eur (E470b)

Tablet Coating:

Titanium dioxide Ph Eur (E171)
Hypromellose 5cps Ph Eur (E464)
Macrogol 400 Ph Eur
Polysorbate 80

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium foil/PVC/PVdC blisters in cartons of 28, 30 or 100 tablets

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Dr. Reddy's Laboratories (UK) Ltd, 6 Riverview Road, Beverley, HU17 0LD

8 MARKETING AUTHORISATION NUMBER(S)

PL08553/0243

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/11/2008

10 DATE OF REVISION OF THE TEXT

04/03/2013