

# SEROXAT CR

## Paroxetine hydrochloride hemihydrate

### QUALITATIVE AND QUANTITATIVE COMPOSITION

Each *SEROXAT CR* (controlled release) tablet contain paroxetine hydrochloride equivalent to 12.5 mg or 25 mg paroxetine free base.

### PHARMACEUTICAL FORM

*12.5 mg tablets*: Yellow, round, biconvex tablets with GSK engraved on one side and 12.5 on the other side.

*25 mg tablets*: Pink, round, biconvex tablets with GSK engraved on one side and 25 on the other side.

### CLINICAL PARTICULARS

#### Indications

##### Adults

##### Major Depressive Disorder:

*SEROXAT CR* tablets are indicated for the treatment of major depressive disorder (MDD).

*SEROXAT CR* has not been systematically evaluated beyond 12 weeks in controlled clinical trials and the physician who elects to use *SEROXAT CR* for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patients.

##### Premenstrual Dysphoric Disorder:

*SEROXAT CR* tablets are indicated for the treatment of premenstrual dysphoric disorder (PMDD).

The effectiveness of *SEROXAT CR* in long-term use, i.e. for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use *SEROXAT CR* for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

##### Social Anxiety Disorder/Social Phobia:

*SEROXAT CR* Tablets are indicated for the treatment of Social Anxiety Disorder, also known as Social Phobia.

The effectiveness of *SEROXAT* CR tablets in the long-term treatment of Social Anxiety Disorder/Social Phobia, i.e. for more than 12 weeks, has not been evaluated in adequate and well-controlled trials. Therefore, the physician who elects to prescribe *SEROXAT* CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

### **Children and adolescents (less than 18 years)**

#### **All Indications:**

*SEROXAT* CR is not indicated for use in children or adolescents aged less than 18 years (*see Warnings and Precautions*).

The efficacy of *SEROXAT* CR tablets has not been studied in children or adolescents aged less than 18 years; however, controlled clinical studies with *SEROXAT* IR (immediate release) tablets in children and adolescents with major depressive disorder failed to demonstrate efficacy, and do not support the use of *SEROXAT* CR in the treatment of depression in this population (*see Warnings and Precautions*).

The safety and efficacy of *SEROXAT* CR in children aged less than 7 years has not been studied.

### **Dosage and Administration**

#### **Adults**

*SEROXAT* CR tablets should be administered as a single daily dose, usually in the morning, with or without food. Patients should be informed that *SEROXAT* CR tablets should not be chewed or crushed, and should be swallowed whole.

#### **Major Depressive Disorder:**

The recommended initial dose is 25 mg/day. Some patients not responding to a 25 mg dose may benefit from dose increases in 12.5 mg/day increments, up to a maximum of 62.5 mg/day according to patient response. Dose changes should occur at intervals of at least 1 week.

As with all antidepressant drugs, dosage should be reviewed and adjusted if necessary within 2 to 3 weeks of initiation of therapy and thereafter as judged clinically appropriate.

Patients with depression should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months.

#### **Premenstrual Dysphoric Disorder:**

The recommended initial dose is 12.5 mg/day. Some patients not responding to a 12.5 mg dose may benefit from having their dose increased to 25 mg/day. Dose changes should occur at intervals of at least 1 week.

Patients with PMDD should be periodically assessed to determine the need for continual treatment.

*SEROXAT* CR may be administered either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle (by starting **14** days prior to the anticipated onset of menstruation through to the first full day of menses and repeating with each cycle), depending on physician assessment. The recommended initial dose is **12.5** mg/day.

### **Social Anxiety Disorder/Social Phobia:**

The recommended initial dose is 12.5 mg daily. Some patients not responding to a 12.5 mg dose may benefit from having dose increases in 12.5 mg/day increments as required, up to a maximum of 37.5 mg/day according to the patient's response. Dose changes should occur at intervals of at least 1 week.

Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

### **General Information**

#### ***Other Populations***

##### ***Elderly:***

Increased plasma concentrations of paroxetine occur in elderly subjects, but the range of concentrations overlaps with that observed in younger subjects.

Dosing should commence at 12.5 mg/day and may be increased up to 50 mg/day.

##### ***Children and adolescents (less than 18 years):***

*SEROXAT* CR is not indicated for use in children or adolescents aged less than 18 years (*see Indications, Warnings and Precautions*).

##### ***Renal/hepatic impairment:***

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30mL/min) or in those with hepatic impairment. The dosage should be restricted to the lower end of the range.

### **DISCONTINUATION OF *SEROXAT* CR**

As with other psychoactive medications, abrupt discontinuation should generally be avoided (*see Warnings and Precautions, Adverse Reactions*). The taper phase regimen used in recent clinical trials involved a decrease in the daily dose by 10 mg/day (equivalent to 12.5 mg/day CR tablets) at weekly intervals.

When a daily dose of 20 mg/day (equivalent to 25 mg/day CR tablets) was reached, patients were continued on this dose for 1 week before treatment was stopped. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

## Contraindications

Known hypersensitivity to paroxetine and excipients.

*SEROXAT* CR tablets should not be used in combination with monoamine oxidase (MAO) inhibitors [including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)] or within 2 weeks of terminating treatment with MAO inhibitors. Likewise, MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with *SEROXAT* CR tablets (*see Interactions*).

*SEROXAT* CR tablets should not be used in combination with thioridazine, because, as with other drugs which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine (*see Interactions*). Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.

*SEROXAT* CR tablets should not be used in combination with pimozide (*see Interactions*).

## Warnings and Precautions

### Children and Adolescents (less than 18 years)

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. In clinical trials of *SEROXAT* CR in children and adolescents, adverse events related to suicidality (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in patients treated with *SEROXAT* CR compared to those treated with placebo (*see Adverse Reactions*). Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

### Clinical worsening and suicide risk in adults

Young adults, especially those with MDD, may be at increased risk for suicidal behaviour during treatment with *SEROXAT* CR. An analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (prospectively defined as aged 18 to 24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25 to 64 years and  $\geq 65$  years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]; all of the events were suicide attempts). However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18 to 30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. This risk persists until significant remission occurs. 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 *SEROXAT CR* is prescribed can be associated with an increased risk of suicidal behaviour, and these conditions may also be co-morbid with MDD. Additionally, patients with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts. All patients should be monitored for clinical worsening (including development of new symptoms) and suicidality throughout treatment, and especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of some symptoms, such as agitation, akathisia or mania, could be related either to the underlying disease state or the drug therapy (*see Akathisia and Mania and Bipolar Disorder below; Adverse Reactions*).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

### **Akathisia**

Rarely, the use of *SEROXAT CR* or other SSRIs has been associated with the development of akathisia, which is characterised by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of *SEROXAT CR*.

### **Serotonin Syndrome/Neuroleptic Malignant Syndrome**

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with *SEROXAT CR* treatment, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with *SEROXAT CR* should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. *SEROXAT CR* should not be used in combination with serotonin-precursors

(such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome (*see Contraindications, Interactions*).

### **Mania and Bipolar disorder**

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that paroxetine is not approved for use in treating bipolar depression. As with all antidepressants, paroxetine should be used with caution in patients with a history of mania.

### **Tamoxifen**

Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with *SEROXAT CR* as a result of paroxetine's irreversible inhibition of CYP2D6 (*see Interactions*). This risk may increase with longer duration of co-administration. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

### **Bone fracture**

Epidemiological studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association with fractures. The risk occurs during treatment and is greatest in the early stages (less than 6 months) of therapy. The possibility of fracture should be considered in the care of patients treated with *SEROXAT CR*.

### **Monoamine Oxidase Inhibitors**

Treatment with *SEROXAT CR* should be initiated cautiously at least two weeks after terminating treatment with MAO inhibitors and dosage of *SEROXAT CR* should be increased gradually until optimal response is reached (*see Contraindications and Interactions*).

### **Renal/hepatic impairment**

Caution is recommended in patients with severe renal impairment or in those with hepatic impairment. (*see Dosage and Administration*).

### **Epilepsy**

As with other antidepressants, *SEROXAT CR* should be used with caution in patients with epilepsy.

### **Seizures**

Overall the incidence of seizures is less than 0.1% in patients treated with paroxetine. The drug should be discontinued in any patient who develops seizures.

### **Electroconvulsive therapy (ECT)**

There is little clinical experience of the concurrent administration of paroxetine with ECT. However, there have been rare reports of prolonged ECT-induced seizures and/or secondary seizures in patients on SSRIs.

### **Glaucoma**

As with other SSRIs, paroxetine can cause mydriasis and should be used with caution in patients with narrow angle glaucoma.

### **Hyponatraemia**

Hyponatraemia has been reported rarely, predominantly in the elderly. The hyponatraemia generally reverses on discontinuation of paroxetine.

### **Haemorrhage**

Skin and mucous membrane bleedings (including gastrointestinal and gynaecological bleeding) have been reported following treatment with paroxetine. Paroxetine should therefore be used with caution in patients concomitantly treated with drugs that give an increased risk for bleeding, and in patients with a known tendency for bleeding or those with predisposing conditions (*see Adverse Reactions*).

### **Cardiac Conditions**

The usual precautions should be observed in patients with cardiac conditions.

### **Symptoms seen on discontinuation of *SEROXAT CR* treatment in adults:**

In clinical trials in adults, adverse events seen on treatment discontinuation occurred in 30% of patients treated with *SEROXAT CR* compared to 20% of patients treated with placebo. The occurrence of discontinuation symptoms is not the same as the drug being addictive or dependence producing as with a substance of abuse.

Dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea have been reported. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within two weeks, though in some individuals they may be prolonged (two to three months or more). It is therefore advised that *SEROXAT CR* should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (*see "Discontinuation of *SEROXAT CR*", Dosage and Administration*).

## **Sexual dysfunction**

Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction (See Adverse Reactions). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

### **Symptoms seen on discontinuation of *SEROXAT CR* treatment in children and adolescents:**

In clinical trials in children and adolescents, adverse events seen on treatment discontinuation occurred in 32% of patients treated with *SEROXAT CR* compared to 24% of patients treated with placebo. Events reported upon discontinuation of *SEROXAT CR* at a frequency of at least 2% of patients and which occurred at a rate at least twice that of placebo were: emotional lability (including suicidal ideation, suicide attempt, mood changes and tearfulness), nervousness, dizziness, nausea and abdominal pain (*see Adverse Reactions*).

### ***SEROXAT CR* 12.5 mg tablets only**

The paroxetine 12.5 mg controlled-release tablet coating (Opadry Yellow: YS-1-2007) contains the colouring agent Sunset Yellow Lake (FD&C Yellow No. 6 aluminium lake), an azo dye which may cause allergic-type reactions.

## **Interactions**

### **Serotonergic drugs**

As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5-HT associated effects (serotonin syndrome: *see Warnings and Precautions*). Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor. Caution should be advised and a closer clinical monitoring is required when serotonergic drugs (such as L-tryptophan, triptans, tramadol, SSRIs, lithium, fentanyl and St. John's Wort – *Hypericum perforatum* – preparations) are combined with *SEROXAT CR*. Concomitant use of *SEROXAT CR* and MAO inhibitors [including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)] is contraindicated (*see Contraindications*).

### **Pimozide**

Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with paroxetine. This is explained by the known CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant use of pimozide and *SEROXAT CR* tablets is contraindicated (*see Contraindications*).

### **Drug metabolising enzymes**

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolising enzymes.



When paroxetine is to be co-administered with a known drug metabolising enzyme inhibitor, consideration should be given to using doses at the lower end of the range.

No initial dosage adjustment is considered necessary when the drug is to be co-administered with known drug metabolising enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin). Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

*Fosamprenavir/ritonavir*: Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

*Procyclidine*: Daily administration of paroxetine increases significantly the plasma levels of procyclidine. If anti-cholinergic effects are seen, the dose of procyclidine should be reduced.

*Anticonvulsants*: carbamazepine, phenytoin, sodium valproate. Concomitant administration does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.

### **Neuromuscular Blockers**

SSRIs may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of mivacurium and suxamethonium.

### **CYP2D6 inhibitory potency of paroxetine:**

As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered drugs metabolised by this enzyme. These include certain tricyclic antidepressants (e.g. amitriptyline, nortriptyline, imipramine and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine, *see Contraindications*), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol.

Tamoxifen has an important active metabolite, endoxifen, which is produced by CYP2D6 and contributes significantly to the efficacy of tamoxifen. Irreversible inhibition of CYP2D6 by paroxetine leads to reduced plasma concentrations of endoxifen (*see Warnings and Precautions*).

### **CYP3A4**

An *in vivo* interaction study involving the co-administration under steady state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. A similar *in vivo* interaction study revealed no effect of paroxetine on alprazolam pharmacokinetics and vice-versa. Concurrent administration of paroxetine with terfenadine, alprazolam and other drugs that are CYP3A4 substrates would not be expected to cause a hazard.

Clinical studies have shown the absorption and pharmacokinetics of paroxetine to be unaffected or only marginally affected (i.e. at a level which warrants no change in dosing regimen) by:

- **food**
- **antacids**
- **digoxin**
- **propranolol**
- **alcohol:** paroxetine does not increase the impairment of mental and motor skills caused by alcohol, however, the concomitant use of *SEROXAT* CR and alcohol is not advised.

#### **Oral anticoagulants:**

A pharmacodynamic interaction between paroxetine and oral anticoagulants may occur. Concomitant use of paroxetine and oral anticoagulants can lead to an increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should be used with caution in patients who are treated with oral anticoagulants.

#### **NSAIDs and acetylsalicylic acid and other antiplatelet agents:**

A pharmacodynamic interaction between paroxetine and NSAIDs/acetylsalicylic acid may occur. Concomitant use of paroxetine and NSAIDs/acetylsalicylic acid can lead to an increased haemorrhagic risk.

Caution is advised in patients taking SSRIs concomitantly with oral anticoagulants, drugs known to affect platelet function or increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

## **Pregnancy and Lactation**

### **Fertility**

Some clinical studies have shown that SSRIs (including *SEROXAT* CR) may affect sperm quality. This effect appears to be reversible following discontinuation of treatment. Changes in sperm quality may affect fertility in some men.

### **Pregnancy**

Animal studies showed reproductive toxicity, but did not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants in the first trimester have reported an increase in the risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septal defects), associated with the use of paroxetine. The data suggest that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population.

The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant, and should only prescribe *SEROXAT CR* if the potential benefit outweighs the potential risk. If a decision is taken to discontinue *SEROXAT CR* treatment in a pregnant woman, the prescriber should consult *Dosage and Administration - Discontinuation of SEROXAT CR* and *Warnings and Precautions – Symptoms seen on discontinuation of SEROXAT CR treatment in adults*.

There have been reports of premature birth in pregnant women exposed to paroxetine or other SSRIs, although a causal relationship with drug therapy has not been established.

Neonates should be observed if maternal use of *SEROXAT CR* continues into the later stages of pregnancy, because there have been reports of complications in neonates exposed to *SEROXAT CR* or other SSRIs late in the third trimester of pregnancy. However, a causal association with drug therapy has not been confirmed. Reported clinical findings have included: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and somnolence. In some instances the reported symptoms were described as neonatal withdrawal symptoms. In a majority of instances the complications were reported to have arisen either immediately or soon (<24 hours) after delivery.

Epidemiological studies have shown that the use of SSRIs (including paroxetine) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The increased risk among infants born to women who used SSRIs late in pregnancy was reported to be four to five times higher than observed in the general population, which has a rate of 1 to 2 per 1000 infants born.

## **Lactation**

Small amounts of paroxetine are excreted into breast milk. In published studies, serum concentrations in breast-fed infants were undetectable (<2 nanograms/mL) or very low (<4 nanograms/mL). No signs of drug effects were observed in these infants. Nevertheless, *SEROXAT CR* should not be used during lactation unless the expected benefits to the mother justify the potential risks for the infant.

## **Effects on Ability to Drive and Use Machines**

Clinical experience has shown that therapy with *SEROXAT CR* is not associated with impairment of cognitive or psychomotor function. However, as with all psychoactive drugs, patients should be cautioned about their ability to drive a car and operate

machinery.

Although paroxetine does not increase the mental and motor skill impairments caused by alcohol, the concomitant use of *SEROXAT* CR and alcohol is not advised.

## **Adverse Reactions**

Some of the adverse experiences listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Adverse drug reactions are listed below by system organ class and frequency.

Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), including isolated reports. Common and uncommon events were generally determined from pooled safety data from a clinical trial population of  $> 8000$  paroxetine-treated patients and are quoted as excess incidence over placebo. Rare and very rare events were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

### **Blood & lymphatic system disorders**

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes.

Very rare: thrombocytopenia.

### **Immune system disorders**

Very rare: severe allergic reactions (including anaphylactoid reactions and angioedema).

### **Endocrine disorders**

Very rare: syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

### **Metabolism & nutrition disorders**

Common: increases in cholesterol levels, decreased appetite.

Rare: hyponatraemia.

Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

### **Psychiatric disorders**

Common: somnolence, insomnia, agitation, abnormal dreams (including nightmares).

Uncommon: confusion, hallucinations.

Rare: manic reactions.

These symptoms may be due to the underlying disease.

### **Nervous system disorders**

Common: dizziness, tremor, headache.

Uncommon: extrapyramidal disorders.

Rare: convulsions, akathisia, restless legs syndrome (RLS).

Very rare: serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering tachycardia and tremor).

Reports of extrapyramidal disorders including oro-facial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medication.

### **Eye disorders**

Common: blurred vision.

Uncommon: mydriasis (*see Warnings and Precautions*).

Very rare: acute glaucoma.

### **Cardiac disorders**

Uncommon: sinus tachycardia.

### **Vascular disorders**

Uncommon: postural hypotension.

### **Respiratory, thoracic and mediastinal disorders**

Common: yawning.

### **Gastrointestinal disorders**

Very common: nausea.

Common: constipation, diarrhoea, vomiting, dry mouth.

Very rare: gastrointestinal bleeding.

### **Hepato-biliary disorders**

Rare: elevation of hepatic enzymes.

Very rare: hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure).

Elevation of hepatic enzymes has been reported. Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice, and/or liver failure) have also been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

### **Skin & subcutaneous tissue disorders**

Common: sweating.

Uncommon: skin rashes.

Very rare: severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria, photosensitivity reactions.

### **Renal & urinary disorders**

Uncommon: urinary retention, urinary incontinence.

### **Reproductive system & breast disorders**

Very common: sexual dysfunction.

Rare: hyperprolactinaemia / galactorrhoea, menstrual disorders (including menorrhagia, metrorrhagia and amenorrhoea).

### **General disorders & administration site conditions**

Common: asthenia, body weight gain.

Very rare: peripheral oedema.

### **Symptoms seen on discontinuation of paroxetine treatment**

Common: dizziness, sensory disturbances, sleep disturbances, anxiety, headache.

Uncommon: agitation, nausea, tremor, confusion, sweating, diarrhoea.

As with many psychoactive medicines, discontinuation of *SEROXAT CR* (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, headache, tremor, confusion, diarrhoea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out (*see Dosage and Administration, Warnings and Precautions*).

### **Adverse Events from Paediatric Clinical Trials**

In paediatric clinical trials the following adverse events, were reported at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia and agitation. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder. Hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age).

In studies that used a tapering regimen (daily dose decreased by 10 mg/day at weekly intervals to a dose of 10 mg/day for one week), symptoms reported during the taper phase or upon discontinuation of *SEROXAT CR* at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo were: emotional lability, nervousness, dizziness, nausea and abdominal pain (*see Warnings and Precautions*).

## **Overdose**

### **Symptoms and Signs**

A wide margin of safety is evident from available overdose information on *SEROXAT CR*.

Experience of *SEROXAT CR* in overdose has indicated that, in addition to those symptoms mentioned under Adverse Reactions, fever, blood pressure changes, involuntary muscle contractions, anxiety and tachycardia have been reported.

Patients have generally recovered without serious sequelae even when doses of up to 2000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely a fatal outcome, but generally when *SEROXAT CR* was taken in conjunction with other psychotropic drugs with or without alcohol.

### **Treatment**

No specific antidote is known.

The treatment should consist of those general measures employed in the management of overdose with any antidepressant. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Patient management should be as clinically indicated, or as recommended by the National Poisons Centre, where available.

## **PHARMACOLOGICAL PROPERTIES**

### **Pharmacodynamics**

#### ***Mechanism of Action***

Paroxetine is a potent and selective inhibitor of serotonin (5-hydroxytryptamine, 5-HT) re-uptake and its antidepressant action and efficacy in the treatment of OCD is thought to be related to its specific inhibition of serotonin re-uptake in brain neurones.

Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants.

Paroxetine has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties.

In accordance with this selective action, *in vitro* studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for  $\alpha_1$ ,  $\alpha_2$  and beta-adrenoceptors, dopamine ( $D_2$ ), 5-HT<sub>1</sub> like, 5-HT<sub>2</sub> and histamine ( $H_1$ ) receptors. This lack of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies which demonstrate lack of CNS depressant and hypotensive properties.

#### ***Pharmacodynamic Effects***

Paroxetine does not impair psychomotor function and does not potentiate the depressant effects of ethanol.

As with other selective 5-HT uptake inhibitors, paroxetine causes symptoms of excessive 5-HT receptor stimulation when administered to animals previously given monoamine oxidase (MAO) inhibitors or tryptophan.

Behavioural and EEG studies indicate that paroxetine is weakly activating at doses generally above those required to inhibit 5-HT uptake. The activating properties are not "amphetamine-like" in nature.

Animal studies indicate that paroxetine is well tolerated by the cardiovascular system.

Paroxetine produces no clinically significant changes in blood pressure, heart rate and ECG after administration to healthy subjects.

Studies indicate that, in contrast to antidepressants which inhibit the uptake of nor-adrenaline, paroxetine has a much reduced propensity to inhibit the antihypertensive effects of guanethidine.

## **Pharmacokinetics**

### ***Absorption***

Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. *SEROXAT* CR tablets control the dissolution rate of paroxetine over a period of four to five hours. In addition to controlling the rate of drug release *in vivo*, an enteric coat delays the start of drug release until *SEROXAT* CR tablets have left the stomach. Compared to immediate release formulations of paroxetine, controlled release tablets have a reduced absorption rate.

Due to first-pass metabolism, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract.

Steady state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled release formulations and pharmacokinetics do not appear to change during long-term therapy.

### ***Distribution***

Paroxetine is extensively distributed into tissues and pharmacokinetic calculations indicate that only 1% of the paroxetine in the body resides in the plasma.

Approximately 95% of the paroxetine present in the plasma is protein bound at therapeutic concentrations.

No correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy).

### ***Metabolism***

The principal metabolites of paroxetine are polar and conjugated products of oxidation and methylation, which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to the therapeutic effects of paroxetine.

Metabolism does not compromise paroxetine's selective action on neuronal 5-HT uptake.

### ***Elimination***

Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in faeces, probably via the bile, of which unchanged paroxetine represents less than 1% of the dose. Thus paroxetine is eliminated almost entirely by metabolism.

Metabolite excretion is biphasic, being initially a result of first-pass metabolism and subsequently controlled by systemic elimination of paroxetine.

The elimination half-life is variable but is generally about one day.



### ***Special Patient Populations***

- **Elderly and Renal/Hepatic Impairment**

Increased plasma concentrations of paroxetine occur in elderly subjects, in subjects with severe renal and in those with hepatic impairment, but the range of plasma concentrations overlaps that of healthy adult subjects.

### **Pre-Clinical Safety Data**

Toxicology studies have been conducted in rhesus monkeys and albino rats; in both, the metabolic pathway is similar to that described for humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to one year duration at doses that were six times higher than the recommended range of clinical doses.

Carcinogenesis: In two year studies conducted in mice and rats, paroxetine had no tumorigenic effect.

Genotoxicity: Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

## **PHARMACEUTICAL PARTICULARS**

### **List of Excipients**

Tablet cores: Hypromellose; Povidone; Lactose Monohydrate; Magnesium Stearate; Colloidal silicon dioxide; Glyceryl behenate; and the following colourants: Yellow Ferric Oxide (12.5 mg tablets) and Red Ferric Oxide (25 mg tablets).

Tablet coating: Methacrylic Acid Copolymer Dispersion; Talc; Triethyl citrate, Opadry Yellow, YS-1-2007 (12.5 mg tablets, includes the colouring agent Sunset Yellow Lake (FD&C Yellow No. 6 aluminium lake)), Opadry Pink, Y-1-1262 (25 mg tablets).

### **Incompatibilities**

There are no known incompatibilities with *SEROXAT* CR tablets.

### **Shelf-Life**

The expiry date is indicated on the packaging.

### **Special Precautions for Storage**

Store at a temperature not exceeding 25°C.

### **Nature and Contents of Container**

*SEROXAT* CR tablets 12.5 mg: PVC/aluminium foil blister packs.

*SEROXAT* CR tablets 25 mg: PVC/aluminium foil blister packs.

## **Instructions for Use/Handling**

No special instructions.

Not all presentations are available in every country.

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