SEROXAT

Paroxetine hydrochloride hemihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

SEROXAT 20 mg tablets: White, film-coated, oval shaped, biconvex tablets with a break line on one side.

Each *SEROXAT* tablet contains paroxetine hydrochloride hemihydrate equivalent to 20 mg paroxetine free base.

CLINICAL INFORMATION

Indications

Adults

Major Depressive Disorder:

SEROXAT is indicated for the treatment of major depressive disorder (MDD).

Results of studies in which patients received *SEROXAT* treatment for up to one year indicate that *SEROXAT* is effective in preventing the relapse of depressive symptoms.

Anxiety Disorders:

Treatment of symptoms and prevention of relapse of Obsessive Compulsive Disorder (OCD).

Treatment of symptoms and prevention of relapse of Panic Disorder With or Without Agoraphobia.

Treatment of Social Anxiety Disorder/Social Phobia.

Treatment of symptoms and prevention of relapse of Generalised Anxiety Disorder.

Treatment of Post-Traumatic Stress Disorder.

Children and adolescents (less than 18 years)

All Indications:

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

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy, and do not support the use of *SEROXAT* in the treatment of depression in this population (*see Warnings and Precautions*).

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

Dosage and Administration

Pharmaceutical form: film-coated tablet

Adults

For oral administration.

It is recommended that *SEROXAT* be administered once daily in the morning with food.

Tablets: The tablets should be swallowed rather than chewed. The 20 mg tablets have functional break lines to allow for breaking the tablets in half to yield 10 mg doses if needed.

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 should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months for depression and may be even longer for OCD and panic disorder. As with many psychoactive medications, abrupt discontinuation should be avoided (*see Adverse Reactions*).

Major Depressive Disorder:

The recommended dose is 20 mg daily. In some patients it may be necessary to increase the dose. This should be done gradually by 10 mg increments to a maximum of 50 mg according to the patient’s response.

Obsessive Compulsive Disorder:

The recommended dose is 40 mg daily. Patients should start on 20 mg daily and the dose may be increased weekly in 10 mg increments. Some patients will benefit from having their dose increased up to a maximum of 60 mg daily.

Panic Disorder:

The recommended dose is 40 mg daily. Patients should be started on 10 mg daily and the dose increased weekly in 10 mg increments according to the patient's response. Patients were dosed in a range of 10 to 60 mg daily in the clinical trials demonstrating the effectiveness of *SEROXAT*. The maximum dosage should not exceed 60 mg daily. As is generally recognised, there is the potential for worsening of panic symptomatology during early treatment of panic disorder; a low initial starting dose is therefore recommended.

Social Anxiety Disorder/Social Phobia:

The recommended dose is 20 mg daily. Patients not responding to a 20 mg dose may benefit from dose increases in 10 mg increments as required, up to a maximum of

50 mg/day. Dose changes should occur at intervals of at least 1 week according to the patient's response.

Generalised Anxiety Disorder:

The recommended dose is 20 mg daily. Some patients not responding to a 20 mg dose may benefit from having dose increases in 10 mg increments as required, up to a maximum of 50 mg/day according to patient's response.

Post-Traumatic Stress Disorder:

The recommended dose is 20 mg daily. Some patients not responding to a 20 mg dose may benefit from having dose increases in 10 mg increments as required, up to a maximum of 50 mg/day according to the patient's response.

General Information

DISCONTINUATION OF *SEROXAT*

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

When a daily dose of 20 mg/day was reached, patients were continued on this dose for one 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.

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 the adult starting dose and may be increased weekly in 10 mg increments to a maximum of 40 mg daily according to the patient's response.

Children and adolescents (less than 18 years):

SEROXAT 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 < 30 mL/min) or in those with hepatic impairment. The recommended dose is 20 mg daily. Incremental dosage, if required, should be restricted

to the lower end of the range.

Contraindications

Known hypersensitivity to paroxetine and excipients.

SEROXAT 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 two weeks of terminating treatment with MAO inhibitors. Likewise, MAO inhibitors should not be introduced within two weeks of cessation of therapy with *SEROXAT* (*see Interactions*).

SEROXAT 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 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* 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* 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 associated with psychiatric disorders

Young adults, especially those with MDD, may be at increased risk for suicidal behaviour during treatment with *SEROXAT*. 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 ≥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* 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* or other selective serotonin reuptake inhibitors (SSRIs) have 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*.

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* 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* 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* 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 *SEROXAT* 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* 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 of therapy. The possibility of fracture should be considered in the care of patients treated with *SEROXAT*.

Monoamine Oxidase Inhibitors

Treatment with *SEROXAT* should be initiated cautiously at least 2 weeks after terminating treatment with MAO inhibitors and dosage of *SEROXAT* should be increased gradually until optimal response is reached (*see Contraindications, 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* should be used with caution in patients with epilepsy.

Seizures

Overall, the incidence of seizures is less than 0.1% in patients treated with *SEROXAT*. *SEROXAT* should be discontinued in any patient who develops seizures.

Glaucoma

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

Electroconvulsive therapy (ECT)

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

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 *SEROXAT*. *SEROXAT* 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*). SSRIs may increase the risk of postpartum haemorrhage (*see Pregnancy and Lactation*).

Cardiac Conditions

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

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

In clinical trials in adults, adverse events seen on treatment discontinuation occurred in 30% of patients treated with *SEROXAT* 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* 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", Dosage and Administration*).

Sexual dysfunction

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* 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* compared to 24% of patients treated with placebo. Events reported upon discontinuation of *SEROXAT* 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*).

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*. Concomitant use of *SEROXAT* 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* 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 *SEROXAT* 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. Co-administration of paroxetine with phenytoin is associated with decreased plasma concentrations of paroxetine and increased adverse experiences. No initial dosage adjustment of paroxetine is considered necessary when these drugs are co-administered; any subsequent dosage adjustment should be guided by clinical effect. Co-administration of paroxetine with other anticonvulsants may also be associated with an increased incidence of adverse experiences.

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* and alcohol is not advised.

Pregnancy and Lactation

Fertility

Some clinical studies have shown that SSRIs (including *SEROXAT*) 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* if the potential benefit outweighs the potential risk. If a decision is taken to discontinue *SEROXAT* treatment in a pregnant woman, the prescriber should consult *Dosage and Administration - Discontinuation of SEROXAT* and *Warnings and Precautions – Symptoms seen on discontinuation of SEROXAT 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.

Observational data have provided evidence of an increased risk (less than two-fold) of postpartum haemorrhage following exposure to SSRIs within one month prior to birth.

Neonates should be observed if maternal use of *SEROXAT* continues into the later stages of pregnancy, because there have been reports of complications in neonates exposed to *SEROXAT* 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 (rate of one to two per 1000 pregnancies).

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* 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

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

Clinical experience has shown that therapy with *SEROXAT* 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.

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 (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), including isolated reports. The

frequencies of 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: transient increases or decreases in blood pressure, postural hypotension.

Transient increases or decreases of blood pressure have been reported following treatment with paroxetine, usually in patients with pre-existing hypertension or anxiety.

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* (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 *SEROXAT* treatment is no longer required, gradual discontinuation by dose tapering be carried out (*see Dosage and Administration and 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* 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 data. Overdose attempts have been reported in patients who took up to 2000 mg alone or in combination with other drugs, including alcohol. Experience of *SEROXAT* 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.

Events such as coma or ECG changes have occasionally been reported and very rarely a fatal outcome, but generally when *SEROXAT* was taken in conjunction with other psychotropic drugs, with or without alcohol.

Treatment

No specific antidote is known.

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

ATC Code

Anatomical Therapeutic Chemical (ATC) code: N06A B05.
Pharmacotherapeutic group: Antidepressants – selective serotonin reuptake inhibitors.

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 and panic disorder is thought to be related to its specific inhibition of serotonin re-uptake in brain neurons.

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

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

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_1 like, 5-HT_2 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.

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

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

Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism.

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 *SEROXAT*.

Elimination

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

Non-Clinical Information

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 INFORMATION

List of Excipients

Tablet core: Calcium phosphate (E341), sodium starch glycolate, magnesium stearate (E572).

Tablet coating: Hydroxypropyl methylcellulose (E464), titanium dioxide (E171), polyethylene glycol and polysorbate 80 (E433).

Shelf-Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Nature and Contents of Container

Tablets: Foil blister packs, child-resistant foil blister packs or polypropylene bottles.

Not all presentations are available locally.

Product Registrant

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Version number: GDS47/IPI32SI

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[GlaxoSmithKline Logo]