# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Seroxat 30 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30 mg paroxetine (as paroxetine hydrochloride hemihydrate).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

Blue, oval shaped biconvex tablets debossed with "SEROXAT 30" on one side and a break bar on the other. The break bar is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of
- Major Depressive Episode
- Obsessive Compulsive Disorder
- Panic Disorder with and without agoraphobia
- Social Anxiety Disorders/Social phobia
- Generalised Anxiety Disorder
- Post-Traumatic Stress Disorder

### 4.2 Posology and method of administration

Posology

*Major depressive episode*

The recommended dose is 20 mg daily. In general, improvement in patients starts after one week but may only become evident from the second week of therapy.

As with all antidepressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. In some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 50 mg a day in 10 mg steps according to the patient's response.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

*Obsessive compulsive disorder (OCD)*

The recommended dose is 40 mg daily. Patients should start on 20 mg/day and the dose may be increased gradually in 10 mg increments to the recommended dose. If after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.

Patients with OCD should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer (see section 5.1).

*Panic disorder*

The recommended dose is 40 mg daily. Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. A low initial starting dose is recommended to minimise the potential worsening of panic symptomatology, which is generally recognised to occur early in the treatment of

this disorder. If after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day.

Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer (see section 5.1).

*Social anxiety disorder/social phobia*
The recommended dose is 20 mg daily.If after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day.Long-term use should be regularly evaluated (see section 5.1).

*Generalised anxiety disorder*
The recommended dose is 20 mg daily.If after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day.Long-term use should be regularly evaluated (see section 5.1).

*Post-traumatic stress disorder*
The recommended dose is 20 mg daily.If after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually in 10 mg steps up to a maximum of 50 mg/day.Long-term use should be regularly evaluated (see section 5.1).

*Withdrawal symptoms seen on discontinuation of paroxetine*
Abrupt discontinuation should be avoided (see sections 4.4 and 4.8). The taper phase regimen used in clinical trials involved decreasing the daily dose by 10 mg at weekly intervals. 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.

*Children and adolescents (7-17 years)*
Paroxetine should not be used for the treatment of children and adolescents as controlled clinical trials have found paroxetine to be associated with increased risk for suicidal behaviour and hostility. In addition, in these trials efficacy has not been adequately demonstrated (see sections 4.4 and 4.8).

*Children aged below 7 years*
The use of paroxetine has not been studied in children less than 7 years. Paroxetine should not be used, as long as safety and efficacy in this age group have not been established.

*Elderly Population*
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. Increasing the dose might be useful in some patients, but the maximum dose should not exceed 40 mg daily.

*Renal/hepatic impairment*
Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance less than 30 ml/min) or in those with hepatic impairment. Therefore, dosage should be restricted to the lower end of the dosage range.

Method of administration
It is recommended that paroxetine is administered once daily in the morning with food. The tablet should be swallowed rather than chewed.

For oral administration

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). In exceptional circumstances, linezolid (an antibiotic which is a reversible non-selective MAOI) can be given in combination with paroxetine provided that

there are facilities for close observation of symptoms of serotonin syndrome and monitoring of blood pressure (see section 4.5).

Treatment with paroxetine can be initiated:
- two weeks after discontinuation of an irreversible MAOI, or
- at least 24hrs after discontinuation of a reversible MAOI (e.g. moclobemide, linezolid, methylthioninium chloride (methylene blue; a preoperative visualising agent which is a reversible non-selective MAOI)).

At least one week should elapse between discontinuation of paroxetine and initiation of therapy with any MAOI.

Paroxetine is contraindicated in combination with thioridazine or with pimozide (see section 4.5).

**4.4 Special warnings and precautions for use**

Treatment with paroxetine should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAO inhibitor. Dosage of paroxetine should be increased gradually until an optimal response is reached (see sections 4.3 and 4.5).

Paediatric population

Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years. 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.

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 until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which paroxetine 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 a significant degree of suicidal ideation prior to commencement of treatment are known to be at 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 medicinal products in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old (see section 5.1).

Close supervision of patients and in particular those at high risk should accompany medicinal product 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 behaviour and to seek medical advice immediately if these symptoms present.

Akathisia/psychomotor restlessness

The use of paroxetine has been associated with the development of akathisia, which is characterized 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.

Serotonin Syndrome/Neuroleptic Malignant Syndrome

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment of paroxetine, particularly when given in combination with other serotonergic and/or neuroleptic medicinal products. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine 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. Paroxetine should not be used in combination with serotonin-precursors (such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome. (See sections 4.3 and 4.5).

Mania
As with all antidepressants, paroxetine should be used with caution in patients with a history of mania. Paroxetine should be discontinued in any patient entering a manic phase.

Renal/hepatic impairment
Caution is recommended in patients with severe renal impairment or in those with hepatic impairment (see section 4.2).

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted. Additionally, there have been studies suggesting that an increase in blood glucose levels may occur when paroxetine and pravastatin are co-administered (see section 4.5).

Epilepsy
As with other antidepressants, paroxetine 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 medicinal product 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.

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

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

QT Prolongation
Cases of QT interval prolongation have been reported during the post-marketing period.

Paroxetine should be used with caution in patients with a (family) history of QT interval prolongation, concomitant use of anti-arrhythmic medications or other medications that may potentially prolong QT interval, relevant pre-existing cardiac disease such as heart failure, ischaemic heart disease, heart block or ventricular arrhythmias, bradycardia, and hypokalaemia or hypomagnesemia (see section 4.3 and 4.5).

Hyponatraemia
Hyponatraemia has been reported rarely, predominantly in the elderly. Caution should also be exercised in those patients at risk of hyponatraemia e.g. from concomitant medications and cirrhosis. The hyponatraemia generally reverses on discontinuation of paroxetine.

Haemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Other haemorrhagic manifestations e.g. gastrointestinal and gynaecological haemorrhage have been reported. Elderly patients may be at an increased risk for non-menses related events of bleeding.

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8).

Caution is advised in patients taking SSRIs concomitantly with oral anticoagulants, medicinal products known to affect platelet function or other medicinal products that may 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 (see section 4.8).

Interaction with tamoxifen
Paroxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, paroxetine should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Withdrawal symptoms seen on discontinuation of paroxetine treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on treatment discontinuation occurred in 30% of patients treated with paroxetine compared to 20% of patients treated with placebo. The occurrence of withdrawal symptoms is not the same as the drug being addictive or dependence producing.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances 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-three months or more). It is therefore advised that paroxetine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs(see section 4.2).

Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

Sodium
Each paroxetine tablet contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

Serotonergic medicinal products
As with other SSRIs, co-administration with serotonergic medicinal products may lead to an incidence of 5-HT associated effects (serotonin syndrome: see section 4.4). Caution should be advised and a closer clinical monitoring is required when serotonergic medicinal products (such as L-tryptophan, triptans, tramadol, linezolid, methylthioninium chloride (methylene blue), SSRIs, lithium, pethidine, buprenorphine, and St. John's Wort – *Hypericum perforatum* – preparations) are combined with paroxetine. Caution is also advised with fentanyl used in general anaesthesia or in the treatment of chronic pain. Concomitant use of paroxetine and MAOIs is contraindicated because of the risk of serotonin syndrome (see section 4.3).

Pimozide
Increased pimozide levels of on average 2.5 times have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with 60 mg paroxetine. This may be 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 paroxetine is contraindicated (see section 4.3).

Medicinal products that prolong the QT interval
The risk of QTc prolongation and/or ventricular arrhythmias (e.g. TdP) may be increased with concomitant use of other medicinal products which prolong the QTc interval (e.g. some antipsychotics) (see section 4.4). Concomitant use of thioridazine and paroxetine is contraindicated, because, as with other medicinal products which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine which can prolong QT interval (see section 4.3).

**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 paroxetine doses at the lower end of the range.

No initial dosage adjustment is considered necessary when the medicinal product is to be co-administered with known drug metabolising enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin) or with fosamprenavir/ritonavir. Any paroxetine dosage adjustment (either after initiation or following discontinuation of an enzyme inducer) should be guided by clinical effect (tolerability and efficacy).

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

Fosamprenavir/ritonavir
Co-administration of fosamprenavir/ritonavir 700/100 mg twice daily with paroxetine 20 mg daily in healthy volunteers for 10 days significantly decreased plasma levels of paroxetine by approximately 55%. The plasma levels of fosamprenavir/ritonavir during co-administration of paroxetine were similar to reference values of other studies, indicating that paroxetine had no significant effect on metabolism of fosamprenavir/ritonavir. There are no data available about the effects of long-term co-administration of paroxetine and fosamprenavir/ritonavir exceeding 10 days.

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.

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 medicinal products metabolised by this enzyme. These include certain tricyclic antidepressants (e.g. clomipramine, nortriptyline, and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine, see section 4.3 and paragraph "Medicinal products that Prolong the QT Interval" in section 4.5 above), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol. It is not recommended to use paroxetine in combination with metoprolol when given in cardiac insufficiency, because of the narrow therapeutic index of metoprolol in this indication.

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including paroxetine) should whenever possible be avoided (see section 4.4).

Alcohol
As with other psychotropic medicinal products patients should be advised to avoid alcohol use while taking paroxetine.

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 (see section 4.4).

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 (see section 4.4).

Caution is advised in patients taking SSRIs, concomitantly with oral anticoagulants, medicinal products 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 that may predispose to bleeding.

Pravastatin

An interaction between paroxetine and pravastatin has been observed in studies suggesting that co-administration of paroxetine and pravastatin may lead to an increase in blood glucose levels. Patients with diabetes mellitus receiving both paroxetine and pravastatin may require dosage adjustment of oral hypoglycaemic agents and/or insulin (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

Pregnancy
Some epidemiological studies suggest an increased risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septum defects), associated with the use of paroxetine during the first trimester. The mechanism is unknown. The data suggest that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is less than 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Paroxetine should only be used during pregnancy when strictly indicated. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant. Abrupt discontinuation should be avoided during pregnancy (see section 4.2).

Observational data indicated an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4 and 4.8).

Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy, particularly the third trimester.

The following symptoms may occur in the neonate after maternal paroxetine use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty in sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

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

Animal studies showed reproductive toxicity, but did not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Breast-feeding
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), and no signs of drug effects were observed in these infants. Since no effects are anticipated, breast-feeding can be considered.

Fertility
Animal data have shown that paroxetine may affect sperm quality (see section 5.3). *In vitro* data with human material may suggest some effect on sperm quality, however, human case reports with some SSRIs (including paroxetine) have shown that an effect on sperm quality appears to be reversible. Impact on human fertility has not been observed so far.

**4.7 Effects on ability to drive and use machines**

Clinical experience has shown that therapy with paroxetine 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 paroxetine and alcohol is not advised.

**4.8 Undesirable effects**

Some of the adverse drug reactions 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 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes (including ecchymosis and gynaecological bleeding), leukopenia.
Very rare: thrombocytopenia.

Immune system disorders
Very rare: severe and potentially fatal allergic reactions (including anaphylactoid reactions and angioedema).

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

Metabolism and nutrition disorders
Common: increases in cholesterol levels, decreased appetite.
Uncommon: altered glycaemic control has been reported in diabetic patients (see section 4.4).
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, anxiety, depersonalisation, panic attacks, akathisia (see section 4.4).
Not known: suicidal ideation, suicidal behaviour, aggression, bruxism.

Cases of suicidal ideation and suicidal behaviour have been reported during paroxetine therapy or early after treatment discontinuation (see section 4.4).
Cases of aggression were observed in post marketing experience.

These symptoms may also be due to the underlying disease.

Nervous system disorders
Common: dizziness, tremor, headache, concentration impaired.
Uncommon: extrapyramidal disorders.
Rare: convulsions, restless legs syndrome (RLS).
Very rare: serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor).
Reports of extrapyramidal disorder 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 section 4.4).
Very rare: acute glaucoma.

Ear and labyrinth disorders
Not known: tinnitus.

Cardiac disorders
Uncommon: sinus tachycardia.
Rare: bradycardia.

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.
Not known: colitis microscopic.

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 have 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 and subcutaneous tissue disorders
Common: sweating.
Uncommon: skin rashes, pruritus
Very rare: severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria, photosensitivity reactions.

Musculoskeletal and connective tissue disorders
Rare: 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.

Renal and urinary disorders
Uncommon: urinary retention, urinary incontinence.

Reproductive system and breast disorders
Very common: sexual dysfunction.
Rare: hyperprolactinaemia/galactorrhoea, menstrual disorders (including menorrhagia, metrorrhagia, amenorrhoea, menstruation delayed and menstruation irregular).
Very rare: priapism.
Not known: postpartum haemorrhage
Postpartum haemorrhage has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6).

General disorder and administration site conditions
Common: asthenia, body weight gain
Very rare: peripheral oedema.

Withdrawal symptoms seen on discontinuation of paroxetine treatment
Common: dizziness, sensory disturbances, sleep disturbances, anxiety, headache.
Uncommon: agitation, nausea, tremor, confusion, sweating, emotional instability, visual disturbances, palpitations, diarrhoea, irritability.

Discontinuation of paroxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported.

Generally, these events are mild to moderate and are self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Adverse events from paediatric clinical trials

The following adverse events were observed:

Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder. Increased hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age.

Additional events that were seen are: decreased appetite, tremor, sweating, hyperkinesia, agitation, emotional lability (including crying and mood fluctuations), bleeding related adverse events, predominantly of the skin and mucous membranes.

Events seen after discontinuation/tapering of paroxetine are: emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide), nervousness, dizziness, nausea and abdominal pain (see section 4.4).

See section 5.1 for more information on paediatric clinical trials.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.
It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance,
Website: www.hpra.ie.

**4.9 Overdose**

Symptoms and Signs

A wide margin of safety is evident from available overdose information on paroxetine.

Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under section 4.8, fever and involuntary muscle contractions 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 with a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic medicinal products, 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. Administration of 20-30 g activated charcoal may be considered if possible within a few hours after overdose intake to decrease absorption of paroxetine. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Patient management should be as clinically indicated.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antidepressants – selective serotonin reuptake inhibitors, ATC code: N06A B05

Mechanism of Action

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake and its antidepressant action and effectiveness in the treatment of OCD, Social Anxiety disorder/Social Phobia, General Anxiety Disorder, Post-Traumatic Stress Disorderand Panic Disorder is thought to be related to its specific inhibition of 5-HT 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 alpha1, alpha2 and beta-adrenoceptors, dopamine (D2), 5-HT1 like, 5-HT2 and histamine (H1) 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 noradrenaline, paroxetine has a much reduced propensity to inhibit the antihypertensive effects of guanethidine.

In the treatment of depressive disorders, paroxetine exhibits comparable efficacy to standard antidepressants.

There is also some evidence that paroxetine may be of therapeutic value in patients who have failed to respond to standard therapy.

Morning dosing with paroxetine does not have any detrimental effect on either the quality or duration of sleep. Moreover, patients are likely to experience improved sleep as they respond to paroxetine therapy.

Adult suicidality analysis
A paroxetine-specific analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (aged 18-24 years) treated with paroxetine compared with placebo (2.19% vs 0.92%). In the older age groups, no such increase was observed. In adults with major depressive disorder (all ages), there was an increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (0.32% vs 0.05%); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults (see section 4.4).

Dose response
In the fixed dose studies there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, there are some clinical data suggesting that up-titrating the dose might be beneficial for some patients.

Long-term efficacy
The long-term efficacy of paroxetine in depression has been demonstrated in a 52-week maintenance study with relapse prevention design: 12% of patients receiving paroxetine (20-40mg daily) relapsed, versus 28% of patients on placebo.

The long-term efficacy of paroxetine in treating obsessive compulsive disorder has been examined in three 24-week maintenance studies with relapse prevention design. One of the three studies achieved a significant difference in the proportion of relapsers between paroxetine (38%) compared to placebo (59%).

The long-term efficacy of paroxetine in treating panic disorder has been demonstrated in a 24-week maintenance study with relapse prevention design: 5% of patients receiving paroxetine (10-40mg daily) relapsed, versus 30% of patients on placebo. This was supported by a 36-week maintenance study.

The long-term efficacy of paroxetine in treating social anxiety disorder and generalised anxiety disorder and Post-Traumatic Stress Disorderhas not been sufficiently demonstrated.

Adverse Events from Paediatric Clinical Trials

In short-term (up to 10-12 weeks) clinical trials in children and adolescents, the following adverse events were observed in paroxetine-treated patients at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo: increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder. Increased hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age. Additional events that were more often seen in the paroxetine compared to placebo group were: decreased appetite, tremor, sweating, hyperkinesia, agitation, emotional lability (including crying and mood fluctuations).

In studies that used a tapering regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo were: emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide), nervousness, dizziness, nausea and abdominal pain (see section 4.4).

In five-parallel group studies with a duration of eight weeks up to eight months of treatment, bleeding related adverse events, predominantly of the skin and mucous membranes, were observed in paroxetine-treated patients at a frequency of 1.74% compared to 0.74% observed in placebo-treated patients.

**5.2 Pharmacokinetic properties**

Absorption
Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. Due to first-pass metabolism, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. Partial saturation of the first-pass effect and reduced plasma clearance occur as the body burden increases with higher single doses or on multiple dosing. This results in disproportionate increases in plasma concentrations of paroxetine and hence pharmacokinetic parameters are not constant, resulting in non-linear kinetics. However, the non-linearity is generally small and is confined to those subjects who achieve low plasma levels at low doses.

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 is protein bound at therapeutic concentrations.

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

Biotransformation
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 paroxetine's therapeutic effects.

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 Population and Renal/Hepatic Impairment*

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

**5.3 Preclinical 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.
Reproduction toxicity studies in rats have shown that paroxetine affects male and female fertility by reducing fertility index and pregnancy rate. In rats, increased pup mortality and delayed ossification were observed. The latter effects were likely related to maternal toxicity and are not considered a direct effect on the foetus/neonate.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Tablet core:
Dibasic calcium phosphate dihydrate (E341)
Sodium starch glycolate (Type A)
Magnesium stearate (E470b)

Tablet coating:
Hypromellose (E464)
Macrogol 400
Polysorbate 80 (E433)
Titanium dioxide (E171)
Indigo carmine (E132)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Do not store above 30ºC.
Store in the original package in order to protect from light.

**6.5 Nature and contents of container**

Child-resistant blister packs comprising opaque polyvinyl chloride (PVC) backed with aluminium foil laminated with paper.
Plastic containers (bottles) made of polypropylene, with polyethylene closures, may also be used.

Pack sizes: 28, 30, 56 and 60 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA1077/097/003

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Date of last renewal: 27th September 2010

**10 DATE OF REVISION OF THE TEXT**

December 2025