

Paroxetine

Core Safety Profile

4.3 Contraindications

Known hypersensitivity to paroxetine or any of the excipients.

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, methylthionium 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 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 section 4.5 Interactions with other medicinal products and other forms of interaction). Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.

Paroxetine should not be used in combination with pimozide (see section 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special Warnings and Special 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 section 4.3 Contraindications and section 4.5 Interactions with other medicinal products and other forms of interaction).

Use in children and adolescents under 18 years of age

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 drugs 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 also section 5.1).

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in 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 drugs. 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 Contraindications and 4.5 Interactions with other medicinal products and other forms of interaction).

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 Posology and Method of Administration)

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

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 drug should be discontinued in any patient who develops seizures.

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.

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 haemorrhage have been reported. Elderly patients may be at an increased risk.

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

Interaction with 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 paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 (see section 4.5). Paroxetine should whenever possible be avoided during tamoxifen use for treatment or prevention of breast cancer.

<Drugs affecting gastric pH>

<In patients receiving oral suspension, the paroxetine plasma concentration may be influenced by gastric pH. *In vitro* data have shown that an acidic environment is required for release of the active drug from the suspension, hence absorption may be reduced in patients with a high gastric pH or achlorhydria, such as after the use of certain drugs (antacid drugs, histamine H₂-receptor antagonists, proton pump inhibitors), in certain disease states (e.g. atrophic gastritis, pernicious anemia, chronic *Helicobacter pylori* infection), and after surgery (vagotomy, gastrectomy). The pH dependency should be taken into account when changing paroxetine formulation (e.g. the plasma paroxetine concentration may decrease after changing from tablet to oral suspension in patients with a high gastric pH). Caution is therefore recommended in patients when initiating or ending treatment with drugs increasing gastric pH. Dose adjustments may be necessary in such situations.>

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 Undesirable effects). 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 2 weeks, though in some individuals they may be prolonged (2-3 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 "Withdrawal Symptoms Seen on Discontinuation of Paroxetine", Section 4.2 Posology and Method of Administration).

<Warnings for excipients>

<Parabens>

<Paroxetine oral suspension contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) (parabens), which are known to cause urticaria; generally delayed type reactions, such as contact dermatitis, but rarely immediate reaction with bronchospasm.>

<Sunset Yellow Colouring Agent>

<Paroxetine oral suspension contains the colouring agent sunset yellow FCF (E110), which may cause allergic reactions.>

<Sorbitol E420>

<Paroxetine oral suspension contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.>

4.5 Interactions with other medicinal products and other forms of interaction

Serotonergic drugs

As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5-HT associated effects (serotonin syndrome: see Section 4.4 Special Warnings and Special Precautions for Use). Caution should be advised and a closer clinical monitoring is required when serotonergic drugs (such as L-tryptophan, triptans, tramadol, linezolid, methylthioninium chloride (methylene blue), SSRIs, lithium, pethidine 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 Contraindications).

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 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 paroxetine 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) 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).

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 drugs 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 Contraindications), 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.

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 section 4.4).

Alcohol

As with other psychotropic drugs 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 Special Warnings and Special Precautions for use)

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 Special warnings and Special Precautions for use)

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

<Drugs affecting gastric pH>

<*In vitro* data have shown that dissociation of paroxetine from the oral suspension is pH-dependant. Therefore, drugs that alter gastric pH (such as antacid drugs, proton pump inhibitors or histamine H2-receptor antagonists) may affect plasma paroxetine concentrations in patients taking the oral suspension (see section 4.4).>

4.6 Pregnancy and Lactation

Fertility

Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality. This effect appears to be reversible following discontinuation of treatment. These studies have not examined impact on fertility but changes in sperm quality may affect fertility in some men.

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 "Withdrawal Symptoms Seen on Discontinuation of Paroxetine", section 4.2 Posology and Method of Administration).

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 5 cases per 1000 pregnancies. In the general population 1 to 2 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 Preclinical Safety Data).

Lactation

Small amounts of paroxetine are excreted into breast milk. In published studies, serum concentrations in breast-fed infants were undetectable (<2 ng/ml) or very low (<4 ng/ml), and no signs of drug effects were observed in these infants. Since no effects are anticipated, breast-feeding can be considered.

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 ($\geq 1/10$), 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.

Blood and lymphatic system disorders

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes (mostly ecchymosis).

Very rare: thrombocytopenia.

Immune system disorders

Very rare: allergic reactions (including urticaria 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.

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).

Frequency not known: suicidal ideation and suicidal behaviour.

Cases of suicidal ideation and suicidal behaviours have been reported during paroxetine therapy or early after treatment discontinuation (see section 4.4).

These symptoms may also be due to the underlying disease.

Nervous system disorders

Very common: concentration impaired.

Common: dizziness, tremor, headache.

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 Special Warnings and Special Precautions for Use).

Very rare: acute glaucoma.

Ear and labyrinth disorders

Frequency 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.

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), photosensitivity reactions.

Renal and urinary disorders

Uncommon: urinary retention, urinary incontinence.

Reproductive system and breast disorders

Very common: sexual dysfunction.

Rare: hyperprolactinaemia/galactorrhoea.

Very rare: priapism.

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.

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 section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

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 Special Warnings and Special Precautions for use).

See section 5.1 for more information on paediatric clinical trials.

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 "Undesirable Effects", 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 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. 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

(...)

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 were: 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 Special Warnings and Special Precautions for use).

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.