PAROXETINE

Paroxetine 20mg (as mesilate) tablet

Each tablet of paroxetine 20mg contains paroxetine mesilate equivalent to 20mg paroxetine base.

Presentation

Paroxetine 20mg tablets are yellow to orange, round shaped, film-coated tablets. The tablets are embossed with "POT 20" on one side. The tablets are scored on both sides.

Uses

Actions

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake and its antidepressant action and efficacy in the treatment of obsessive compulsive disorder (OCD), panic disorder and social anxiety disorder/social phobia are thought to be related to its specific inhibition of 5HT uptake in brain neurones. In vitro studies have indicated that, in contract to tricyclic antidepressants, paroxetine has little affinity for $alpha_1$-, $alpha_2$- and beta-adrenoreceptors, dopamine (D_2), 5-HT_1-like, 5-HT_2 and histamine (H_1) receptors. This lack of interaction with postsynaptic receptors in vitro is substantiated by in vivo studies that demonstrate a lack of CNS depressant and hypotensive properties. Paroxetine has a low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties.

Because the relative potencies of paroxetine's major metabolites are at most one-fiftieth of the parent compound, it is most unlikely that they contribute to the therapeutic effect of paroxetine.

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 inhibitors (MAOIs) or tryptophan. Behavioural and electronencephalographic (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.

Paroxetine does not impair psychomotor function and does not potentiate the depressant effects of ethanol. Animal studies indicate that paroxetine is well tolerated by the cardiovascular system, and in healthy subjects, paroxetine produces no clinically significant changes in blood pressure, heart rate and electrocardiograph (ECG).

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.

In general, improvement in patients starts after one week but does not become superior to placebo until the second week of therapy. Nevertheless, there is no convincing evidence to support a relationship between plasma concentrations of paroxetine and clinical efficacy.

Paroxetine is effective in improving depression and suicidal ideation concurrently during the first few weeks of 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 improvement of sleep as they respond to paroxetine therapy. Where it is clinical practice to co-prescribe short acting hypnotics with antidepressants, no additional adverse events have been recorded.

Paroxetine, in addition to its significant effects, can improve associated symptoms of anxiety.

Pharmacokinetics

Absorption

Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. As a consequence, 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 dosing or on multiple dosing. This results in disproportionate increases in plasma concentrations of paroxetine and hence pharmacokinetic parameters are not constant, resulting in nonlinear kinetics. These properties are a consequence of the fact that one of the enzymes that metabolises paroxetine is the readily saturable cytochrome P450 enzyme (CYP2D6). However, because this enzyme becomes saturated early on following commencement of paroxetine treatment, the nonlinearity observed during a subsequent dose increase is generally small and is confined to those subjects who achieve low plasma levels at low doses.

The relative bioavailability of paroxetine 20mg tablets is similar to paroxetine hydrochloride 20 mg tablets.

		Paroxetine mesilate	**Paroxetine Hydrochloride**
		20 mg tablet	
C_{max} (ng/mL)	Mean ± SD	4.08 ± 3.34	4.24 ± 3.48
$AUC_{(O-in)}$ (ng.h/mL)	Mean ± SD	90.61 ± 124.63	95.28 ± 131.42
t_{max} (h)	Median (range)	6.00 (1.5 - 8.0)	5.99 (2.0 - 10.0)
$T_{½}$ (h)	Mean ± SD	13.8 ± 6.2	13.6 ± 4.8

In the literature, after a single oral dose of 20 mg, peak plasma levels up to 33 ng/mL have been reported.

Distribution

Paroxetine is distributed throughout the body including the central nervous system. Approximately 95% of the paroxetine present in the plasma is protein bound at therapeutic concentrations.

Metabolism

Paroxetine is extensively metabolised after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulphate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than one-fiftieth the potency of the parent compound at inhibiting serotonin uptake.

The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. At steady state, when CYP2D6 is essentially saturated, paroxetine clearance is governed by alternate P450 isoenzymes which, unlike CYP2D6, are not saturable at clinical doses (as evidenced by linear pharmacokinetics in CYP2D6 deficient individuals).

Because of the involvement of CYP2D6 in the metabolic clearance of paroxetine, considerable variation can occur in the plasma concentrations and clinical effect (adverse experiences and efficacy). However, no correlation has been found between paroxetine plasma concentrations and clinical effect. Increased plasma concentrations of paroxetine occur in elderly subjects and in those subjects with severe renal and hepatic impairment, but the range of plasma concentrations overlaps that of healthy adult subjects.

Excretion

Approximately 64% of the dose is excreted in the urine; urinary excretion of unchanged paroxetine is generally less than 2% of dose. About 36% of the dose is excreted in the faeces, probably via the bile; faecal excretion of 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.

Although the elimination half-life reported in the literature after a single 20mg dose is generally about 16-21 hours, a wide range of 3 to 65 hours has been reported. Steady state systemic levels are attained by seven to 14 days after starting treatment and pharmacokinetics do not appear to change during long-term therapy.

Considerable variation can occur in the plasma concentration achieved between individuals, possibly due to variable first-pass effect and variability in clearance.

Indications

FOR Adults and APPROVED INDICATIONS USE ONLY

Depression

Depression of all types, including reactive and severe depression and depression accompanied by anxiety.

Paroxetine is indicated for the prevention of relapse and also recurrence of further depressive episodes.

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

In general, improvement in patients starts after one week but does not become superior to placebo until the second week of therapy.

Paroxetine, in addition to its significant antidepressant effects, also improves associated symptoms of anxiety.

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.

Where it is clinical practice to co-prescribe short-acting hypnotics with antidepressants, no additional adverse events have been recorded.

Paroxetine is effective in improving depression and suicidal ideation concurrently during the first few weeks of therapy.

Long term treatment with paroxetine has shown that efficacy is maintained for periods of at least one year.

Obsessive Compulsive Disorder

Paroxetine is indicated for the treatment of Obsessive Compulsive Disorder (OCD).

In a placebo-controlled trial, the efficacy of paroxetine in the treatment of OCD has been maintained for at least 1 year.

Panic Disorder

Paroxetine is indicated for the treatment of Panic Disorder with and without agoraphobia.

The combination of paroxetine and cognitive-behavioural therapy has been shown to be significantly more effective than cognitive-behavioural therapy alone in the treatment of Panic Disorder.

In a placebo-controlled trial, the efficacy of paroxetine in the treatment of Panic Disorder has been maintained for up to 1 year.

Social Anxiety Disorder/Social Phobia

Paroxetine has been shown to be effective in the treatment of Social Anxiety Disorder/Social Phobia.

Generalised Anxiety Disorder

Paroxetine has been shown to be effective in the treatment of Generalised Anxiety Disorder.

In a placebo-controlled trial, the efficacy of paroxetine in the treatment of Generalised Anxiety Disorder has been maintained for up to 32 weeks.

Posttraumatic Stress Disorder

Paroxetine has been shown to be effective in the treatment of Post-traumatic Stress Disorder.

Children and adolescents (<18 years)

Paroxetine is not indicated for use in children or adolescents aged <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 paroxetine in the treatment of depression in this population (see Warnings and Precautions).

The safety and efficacy of paroxetine in children aged <7 years has not been studied.

Dosage and Administration

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

Depression

The recommended dose is 20mg (one tablet) daily. Many patients will respond to a 20mg daily dose. Patients not responding to a 20mg dose may benefit from dose increases in 10mg /day increments, up to a maximum of 50 mg/day according to the patient's response.

As with all antidepressant drugs, dosage should be reviewed and adjusted if necessary within two or three weeks of initiation of therapy and thereafter as judged clinically appropriate. Dosage changes should occur at intervals of at least one week.

It is generally recommended that a course of antidepressant drug treatment should continue for a sufficient period, often for several months. There is no body of evidence available to answer the question of how long the patient treated with paroxetine should remain on it. It is generally agreed that acute episodes of depression require several months or longer of sustained drug therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain or sustain euthymia is unknown.

Systematic evaluation of paroxetine showed that efficacy was maintained for periods of up to one year.

Obsessive compulsive disorder

The recommended dose of paroxetine is 40 mg (two tablets) daily. Patients should start on 20 mg and the dose can be increased weekly in 10 mg increments. Some patients will benefit from having their dose increased up to a maximum of 60 mg/day.

Long-term maintenance of efficacy was demonstrated in a six month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see *Clinical Trials*). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Patients with OCD should be treated for a sufficient period to ensure that they are free from symptoms.

Panic disorder

The recommended dose is 40 mg daily. Patients should be started on 10 mg/day and the dose increased weekly in 10 mg increments according to the patient's response. Some patients may benefit from having their dose increased to a maximum of 60 mg/day.

A low starting dose and slow dosage increase reduce the risk of an initial transient increase in anxiety, which is generally recognised to occur early in the treatment of this disorder.

Long-term maintenance of efficacy was demonstrated in two studies, the first a three month relapse prevention trial and the second a 36 week extension study (see *Clinical trials*). In the relapse prevention trial patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo. Panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social anxiety disorder/social phobia

The recommended dose is 20 mg (one tablet) daily. Some patients may benefit from having their dose increased up to a maximum of 50 mg/day. Patients should start on 20 mg and, according to the patient's response, the dose can be increased weekly in 10 mg increments. The lowest dose of paroxetine studied in clinical trials (20 mg) produced a statistically significant superior response to placebo.

Generalised Anxiety Disorder

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

Posttraumatic Stress Disorder

For the majority of patients, the recommended starting and maintenance dose is 20mg daily. However some patients not responding to a 20mg dose may benefit from having dose increases in 10mg increments as required, up to a maximum of 50mg/day according to the patient's response. The use of Paroxetine beyond 12 weeks has not been investigated in clinical trials.

Use in the 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 up to 40 mg daily. Dosing should not exceed 40 mg daily.

Elderly patients should be initiated and maintained at the lowest daily dosage of paroxetine that is associated with clinical efficacy.

Use in Children and Adolescents (under 18 years of age)

Safety and efficacy have not been established in this population. Consequently, paroxetine should not be used in patients under 18 years of age (See Warnings and Precautions).

Impaired renal and hepatic function

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

Discontinuation of treatment

Withdrawal reactions have been noted one to four days after abrupt cessation; these effects were observed commonly in two long-term studies for panic disorder. Paroxetine should not normally be discontinued abruptly. When paroxetine is to be discontinued, the dose should be tapered. 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. As with many psychoactive medicines, abrupt discontinuation may lead to systems such as dizziness, sensory disturbances, sleep disturbances, tremor, agitation or anxiety, nausea and sweating.

Prolonged treatment

Doctors who elect to prescribe paroxetine for an extended period should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Contraindications

Paroxetine is contra-indicated in patients known to have a hypersensitivity to paroxetine or to any of the excipients used in the tablet.

Concomitant use of paroxetine in patients receiving monoamine oxidase (MAO) inhibitors is contra-indicated and a washout period of at least 2 weeks is recommended when changing from MAO inhibitor therapy to paroxetine or vice versa (see Warnings and Precautions).

Paroxetine should not be used in combination with thioriazine, 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 torsade de pointes, and sudden death.

Pimozide

Concomitant use of paroxetine and pimozide causes an increase in plasma pimozide levels and thus may increase the risk of QTc prolongation and/or severe arrythmias such as torsades de pointes.

Warnings and Precautions

QTc prolongation /TdP

Cases of QTc prolongation and Torsades de Pointes (TdP), have been reported during the post-marketing use of paroxetine. The majority of reports occurred in patients with other risk factors for QTc prolongation /TdP.

Therefore paroxetine should be used with caution in patients with risk factors for QTc prolongation including congenital long QT syndrome, age >65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of paroxetine, and the concomitant use of other QT prolonging medicines (see Interactions). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

In high risk patients (eg congenital long QT syndrome or multiple risk factors), an ECG should be performed prior to starting treatment, at steady state, after dose increases o after starting any potentially interacting medicine. Electrolytes should be monitored periodically. An ECG should also be performed in all patients experiencing symptoms that could be indicative of an arrhythmia (eg dizziness, palpitations, syncope or new onset seizures).

Consideration should be given to stopping paroxetine treatment or reducing the dose if the QTc interval is > 500ms or increases by >60ms.

Diabetes

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

Bone Fractures

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.

Alcohol

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

The possibility of a suicide attempt is inherent to depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for paroxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Clinical worsening and Suicide Risk

Patients of any age with Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until such improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly. (See "Dosage and Administration"- "*Discontinuation of Treatment*")

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Note: The Medicines Act 1981 allows a doctor to prescribe a medicine for any indication regardless of whether it is approved or not for that indication. There are limitations to this authority embedded in the Code of Health and Disability Services Consumers' Rights 1996. Unapproved use of medicines must comply with this Code, which states that the patient has the right to treatment of an appropriate ethical and professional standard, and the doctor has the responsibility to ensure that treatment, whether approved or unapproved, meets this standard. The patient also has the right to be fully informed. If the use of a medicine is unapproved, the patient should be so advised and the doctor should be frank about the level of evidence for the medicine's efficacy as well as any safety concerns. The doctor must fully discuss the risk/benefit issues with the patient/parent, and in appropriate circumstances this may lead to the use of an antidepressant with informed consent. (For more information on unapproved use of medicines see Medsafe article:
www.medsafe.govt.nz/Profs/RIss/unapp.asp)

Akathisia

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

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 any antidepressant alone may increase the likelihood 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. It should be noted that paroxetine is not approved for use in treating bipolar depression.

Information for Patients and Families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Monoamine oxidase inhibitors

As with most antidepressants, paroxetine should not be used in combination with MAOIs or within two weeks of terminating treatments with MAOIs. Thereafter, treatment should be initiated cautiously and dosage increased gradually until optimal response is reached.

MAOIs should not be introduced within two weeks of cessation of therapy with paroxetine.

Tricyclic antidepressants

Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with Paroxetine 20mg because paroxetine may inhibit TCA metabolism via cytochrome P450 enzyme 2D6. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with Paroxetine.

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 Interactions with other Drugs).

Activation of mania/hypomania

As with all antidepressants, paroxetine should be used with caution in patients with a history of mania or hypomania.

Oral anticoagulants

Paroxetine should administered with great caution to patients receiving oral anticoagulants (see *Interactions with Other Drugs*).

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 *Interaction* section). 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 inhibitors.

Tryptophan

As adverse experiences have been reported when tryptophan was administered with another selective 5-HT uptake inhibitor, paroxetine should not be used in combination with tryptophan medication (see *Interactions with Other Drugs)*.

Cardiac Conditions

The usual precautions should be observed in patients with cardiac conditions. There is limited experience concerning the use of paroxetine in patients with recent myocardial infarction or unstable heart disease.

Epilepsy

As with other antidepressants, paroxetine should be used with caution in patients with epilepsy or a history of convulsive disorders.

Seizures

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

Electroconvulsive therapy (ECT)

The efficacy and safety of the concurrent use of paroxetine 20mg and ECT have not been studied.

Glaucoma

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

Haemorrage

Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, haematoma, epstaxis, vaginal bleeding and gastrointestinal bleeding). This risk may be potentiated by concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin or other medicines that affect coagulation. Paroxetine 20mg should therefore be used with caution in patients concomitantly treated with medicines that increase the risk of bleeding or in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastro protection should be considered for high risk patients.

Alcohol

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

Children and Adolescents (under 18 years of age)

In clinical trials, adverse events related to suicidality (suicidal thoughts and suicidal behaviours) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with SSRIs (and venlafaxine) compared to those treated with placebo. Long term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Use in the elderly

See Dosage and Administration.

Carcinogenesis, mutagenesis

In two year studies conducted in mice and rats, paroxetine had no tumorigenic effect, and no genotoxicity effects were observed in a battery of *in vitro* and *in vivo* tests.

Impairment of fertility

Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function (i.e. reduced pregnancy rate, increased pre- and post-implantation losses, decreased viability of pups) was found in reproduction studies in rats at paroxetine doses of 13 mg/kg and above. Vacuolation of epididymal tubular epithelium and atrophic changes in the sominiferous tubules of the testes with arrested spermatogenesis occurred in male rats at doses of 25 mg/kg/day in toxicity studies.

Symptoms seen on discontinuation of paroxetine treatment in adults

In clinicals trials in adults, 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 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 and electric shock sensations), 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 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 "Dosage and Administration" - "*Discontinuation of Treatment*",).

Symptoms seen on discontinuation of paroxetine 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 paroxetine compared to 24% of patients treated with placebo. Events reported upon discontinuation of paroxetine at a frequency of at least 2% of patients and which occured 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 Effects).

Use in Pregnancy

Category C

Paroxetine should not be used during pregnancy, unless the potential benefit outweighs the possible risk. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant.

If a decision is taken to discontinue paroxetine treatment in a pregnant woman, the prescriber should consult Dosage and Administration - Discontinuation of Paroxetine and Warnings and Precautions - Symptoms seen on discontinuation of paroxetine treatment in adults.

Epidemiological studies have shown infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations.

A recent retrospective US epidemiological study of 5,956 infants born to women exposed to paroxetine or other antidepressants during the first trimester of pregnancy showed an increased risk of major congenital malformations overall for paroxetine compared to other antidepressants (odds ratio1.8; 95% confidence interval1.2 - 2.8). There was also an increased risk of cardiovascular malformations for paroxetine compared to other antidepressants (odds ratio1.5; 95% confidence interval 0.8 - 2.9). These figures excluded

women exposed to both antidepressants and teratogenic drugs. The majority of cardiovascular malformations were ventricular septal defects.

The prevalence of congenital malformations as a whole and cardiovascular malformation alone in these infants was 4% and 1.5% for paroxetine versus. 2% and 1% for other antidepressants respectively. These rates compare with those in the general population of 3% for all congenital malformation and 1% for cardiovascular malformation. [Centers for Disease Control and Prevention, USA and Metropolitan Atlanta Birth Congenital Defects Program Data (MACDP)].

A study based on the Swedish Medical Birth Register evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRI's including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations compared to the entire registry population (odds ratio 1.8; 95% confidence interval 1.1 - 2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was approximately 2% versus 1% in the entire registry population. No increase in the overall risk for congenital malformations was observed in these infants exposed to paroxetine.

Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy, because there have been reports of complications in neonates exposed to paroxetine 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, hypoglycemia, 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 4 to 5 times higher than observed in the general population (rate of 1 to 2 per 1000 pregnancies).

Animal studies have not shown any teratogenic or selective embryotoxic effects, and data on a limited number of exposed pregnancies in humans provide no indication of an increased risk of congenital malformations in the newborn. There have been reports of premature birth in pregnant women exposed to paroxetine or others SSRIs, although a causal relationship with drug therapy has not been established. Paroxetine should not be used during pregnancy unless the potential benefit outweighs the possible risk.

Use in 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). No signs of drug effects were observed in these infants. Nevertheless, paroxetine should not be used during lactation unless the expected benefits to the mother justify the potential risks for the infant.

Effect on the ability to drive or operate machinery

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 or operate machinery.

Other: 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 6 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.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to this medicine's efficacy and safety when used in the treatment regimen proposed.

Adverse Effects

Adverse experiences with paroxetine are generally mild in nature and do not affect the patient's lifestyle. Adverse experiences may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy. 13% of paroxetine (n = 2,963) treated patients in worldwide short-term clinical trials for depression discontinued treatment due to an adverse experience, compared to 5% receiving placebo (n = 554).

In addition, 11.8% (65/542) and 9.4% (44/462) of paroxetine patients withdrew from worldwide trials in obsessive compulsive disorder (OCD) (versus placebo, 21/265, 7.9%) and panic disorder (versus placebo, 32/324, 9.9%), respectively.

The most commonly observed adverse events associated with the use of paroxetine in clinical trials and not seen at an equivalent incidence among placebo treated patients were nausea, somnolence, sweating, tremor, asthenia, dry mouth, insomnia, sexual dysfunction, dizziness, constipation, diarrhoea and decreased appetite.

Paroxetine is less likely than tricyclic antidepressants to be associated with dry mouth, constipation and somnolence.

The following adverse events were observed during the clinical trial programs for depression, OCD and panic disorder. All adverse experiences are included in the list except those reported in terms so general as to be uninformative and those experiences for which the drug cause was remote. It should however be noted that causality has not necessarily been established, and that patients enrolled in the clinical trials may have been generally healthier than the general patient population. Events are listed within body systems and categorised by frequency according to the following definitions: common events reported at a frequency of greater than or equal to 1/100 patients; uncommon events reported at a frequency of less

than 1/100 but greater than or equal to 1/1,000 patients; rare events reported at a frequency of less than 1/1,000 patients.

Key to symbols
* = Incidence corrected for gender.
+ = Adverse experiences reported more frequently in OCD versus depression clinical trials
# = Adverse experiences reported in OCD clinical trials.
** = Adverse experiences reported more frequently in panic disorder versus depression clinical trials.
^ = Adverse experiences reported in panic disorder clinical trials.

Body as a whole

Common: headache, asthenia, abdominal pain, fever, chest pain, trauma, back pain, malaise, pain.

Uncommon: allergic reactions, chills +**, face oedema, infection +, candidiasis, neck pain, overdose.

Rare: abnormal laboratory value, abscess, adrenergic syndrome, cellulitis, chills and fever, cyst, hernia, intentional overdose, neck rigidity, pelvic pain, peritonitis, substernal chest pain, ulcer.

Cardiovascular

Common: palpitations, vasodilatation, postural hypotension, hypertension, syncope, tachycardia.

Uncommon: bradycardia, conduction abnormalities, abnormal electrocardiograph, hypotension, migraine+, ventricular extrasystoles.

Rare: angina pectoris, arrhythmia, atrial arrhythmia, atrial fibrillation, bundle branch block, cerebral ischaemia, cerebrovascular accident, congestive heart failure, extraystoles, low cardiac output, myocardial infarct, myocardial ischaemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis ^, thrombosis, varicose vein, vascular headache.

Gastrointestinal

Common: nausea, dry mouth, constipation, diarrhoea, decreased appetite, flatulence, vomiting, oropharyngeal disorder, dyspepsia, increased appetite, gastrointestinal disorder #, tooth disorder #, stomatitis #

Uncommon: bruxism, buccal cavity disorders, dysphagia, eructation, gastroenteritis, gastrointestinal flu, glossitis, increased salivation, abnormal liver function tests +, mouth ulceration, rectal haemorrhage.

Rare: aphthous stomatitis, bloody diarrhoea, bulimia, colitis, duodenitis, oesophagitis, faecal impaction, faecal incontinence, gastritis, gingivitis +, haematemesis, hepatitis, ileus, jaundice, melaena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue oedema, tooth caries, tooth malformation ^.

Haematological

Uncommon: anaemia, leucopenia, lymphadenopathy, white blood cell abnormality. Abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis haematomas, vaginal bleeding and gastrointestinal bleeding.

Rare: eosinophilia, iron deficiency anaemia, leucocytosis, lymphoedema, lymphocytosis, microcytic anaemia, monocytosis, normocytic anaemia.

Endocrine

Rare: diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis.

Metabolic/nutritional

Common: weight gain #^, weight loss #.

Uncommon: oedema, hyperglycaemia, peripheral oedema, thirst.

Rare: increased alkaline phosphatase +, bilirubinaemia, dehydration, gout, hypercholesterolaemia, hyperphosphataemia^, hypocalcaemia, hypoglycaemia, hypokalaemia, hyponatraemia, obesity, increased AST, increased ALT.

Musculoskeletal

Common: myopathy, myalgia, myasthenia.

Uncommon: arthralgia +, arthritis, traumatic fracture.

Rare: arthrosis, bursitis, cartilage disorder, myositis, osteoporosis, tetany.

Nervous System

Common: somnolence, insomnia, dizziness, tremor, nervousness, anxiety, paraesthesia, decreased libido, agitation, drugged feeling, myoclonus, CNS stimulation, confusion, impaired concentration, depression, emotional liability, vertigo, abnormal dreams #, hyperthesia +.

Uncommon: abnormal thinking +, akinesia, alcohol abuse, amnesia +, ataxia, convulsion, depersonalisation +, hallucinations, hyperkinesia +, hypertonia +, incoordination, lack of emotion, manic reaction, paranoid reaction.

Rare: abnormal electroencephalograph, abnormal gait, antisocial reaction, choreoathetosis, circumoral paraesthesia, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsions, hostility +, hyperalgesia, hypokinesia, hysteria, increased libido, manic depressive reaction, meningitis,

myelitis, neuralgia, neuropathy, nystagmus, psychosis, psychotic depression, increased reflexes, stupor, withdrawal syndrome.

Others: suicidal ideation and suicidal behaviour, extra pyramidal disorders, aggression.

Reversible Cerebral vasoconstriction syndrome (thunderclap headache) has been associated with serotonergic agents such as SSRIs or triptans.

Respiratory

Common: respiratory disorder, yawning, pharyngitis, increased cough, rhinitis.

Uncommon: asthma, bronchitis, dyspnoea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis +.

Rare: hiccup, lung fibrosis, increased sputum, voice alteration, emphysema ^, pulmonary oedema ^.

Dermatological

Common: sweating, rash, pruritus, sweat gland disorder #.

Uncommon: acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, herpes simplex, urticaria.

Rare: angioedema, contact dermatitis, erythema, nodosum, herpes zoster, hirsutism ^, maculopapular rash, photosensitivity, skin discoloration, skin ulcer.

Special senses

Common: blurred vision, abnormal vision #, taste perversion.

Uncommon: abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, tinnitus +, keratoconjunctivitis #.

Rare: amblyopia, specified cataract, conjunctival oedema, corneal lesion, corneal ulcer, exophthalmos, eye haemorrhage, glaucoma, hyperacusis, otitis externa, photophobia, retinal haemorrhage, taste loss, anisocoria, deafness.

Genitourinary

Common: abnormal ejaculation *, urinary frequency, female/male genital disorder *, impaired urination, impotence *.

Uncommon: abortion *, amenorrhoea *, breast pain *, cystitis, dysmenorrhoea +*, dysuria, menorrhagia *, nocturia, polyuria, urinary incontinence, urinary retention, urinary tract infection +**, urinary urgency, vaginitis +*.

Rare: breast atrophy *, female lactation *, haematuria, renal calculus, abnormal renal function, kidney pain, mastitis *, nephritis, oliguria, urethritis, urine abnormality, vaginal candidiasis *.

Rare events occurring during post-marketing surveillance

QTc prolongation and Torsafes de Pointes have been reported during post-marketing surveillance.

The following adverse events have been reported rarely: dizziness, rash, acute glaucoma, urinary retention, peripheral and facial oedema, tachycardia, thrombocytopenia, neuroleptic malignant syndrome, serotonin syndrome and symptoms suggestive of hyperprolactinaemia / galactorrhoea.

Hyponatraemia has been reported rarely, predominantly in the elderly, and in some cases may be associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The hyponatraemia generally reverses on discontinuation of paroxetine.

Elevation of hepatic enzymes has been reported. Serious hepatic abnormalities have been reported rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

Occasional reports of extrapyramidal disorders including orofacial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medication.

As with other SSRIs, transient increases or decreases in blood pressure have been reported following treatment with paroxetine, usually in patients with pre-existing hypertension or anxiety.

Withdrawal reactions

Some patients will experience withdrawal effects, and dosage may need to be tapered during withdrawal. (See "Dosage and Administration" - "*Discontinuation of Treatment*").As with many psychoactive medicines, abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances, sleep disturbances, tremor, agitation or anxiety, lethargy, nausea and sweating.

Interactions

Medicines that prolong the QT interval

The risk of QTc prolongation and/or ventricular arrhythmias (eg Torsades de pointes) is increased with concomitant use of other medicines which prolong that QTc interval (eg some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval (see WARNINGs-QTc Prolongation and Torsade de Pointes).

Interactive Effects on Paroxetine

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 paroxetine and alcohol is not advised.

Warfarin

A double-blind parallel group study was performed in which healthy male volunteers were given daily doses of warfarin until a stable prothrombin time (measured as an INR) was achieved. There was no clinically or statistically significant change in INR in subjects who were then dosed with paroxetine or placebo, in addition to warfarin, for 28 days.

The following tabulated results of this study show that the healthy volunteers who received paroxetine had no significant differences in coagulation factors or the prothrombin time, measured as an INR. This suggests that paroxetine has no effect on warfarin metabolism and therefore, it would not be expected that patients receiving warfarin therapy would develop an overdosage effect when they start therapy with paroxetine. With respect to the platelet function, the overall screening tests and bleeding time were unchanged after paroxetine therapy. Pharmacokinetics analysis has shown that there appears to be no effect of paroxetine on plasma concentrations between paroxetine-dosed and placebo-dosed subjects.

INR and bleeding time results in warfarin treated subjects given paroxetine or placebo:

		Paroxetine mean		**Placebo mean**			
Parameter	**N**	**Day 1**	**Day 28**	**Day 1**	**Day 28**	**Paroxetine Placebo***	**95% CI**
INR	21	1.58	1.30	1.50	1.36	0.92	(0.77-1.09)
Bleed Time (min)	23	4.58	4.86	6.15	5.81	1.00	(0.82-1.23)

*Point estimates and 95% confidence intervals are adjusted for baseline (day 1) by covariate analysis.

Drugs affecting hepatic metabolism

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolising enzymes. For example, cimetidine, a known drug metabolising enzyme inhibitor, can increase the bioavailability of paroxetine, whereas phenytoin, a known drug metabolising enzyme inducer, can decrease it.

When paroxetine is to be co-administered with a known drug metabolising enzyme inhibitor, consideration should be given to using doses at the lower end of the range. No initial dosage adjustment is considered necessary when the drug is to be co-administered with known drug metabolising enzyme inducer (e.g. carbamazepine, phenytoin, sodium valproate). Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

Medicines that interfere with haemostasis (NSAIDs, aspirin, warfain, etc.)

Serotonin release by platelets plays an important role in haemostasis. There is an association between the use of psychotrophic drugs that interfere with serotonin reuptake and the occurance of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with Paroxetine.

Phenytoin

Co-administration of paroxetine and phenytoin is associated with decreased plasma concentrations of paroxetine in healthy volunteers and increased adverse experiences. No initial dosage adjustments of paroxetine are considered necessary when these drugs are co-administered, any subsequent adjustments should be guided by clinical effect. Co-administration of paroxetine with other anticonvulsants may also be associated with an increased incidence of adverse experiences.

Drugs metabolised by cytochrome P450 2D6

As with other antidepressants, including other selective serotonin reuptake inhibitors (SSRIs), paroxetine inhibits the specific hepatic cytochrome P450 enzyme (CYP2D6).

This may lead to enhanced plasma levels of those co-administered drugs which are metabolised to a significant extent by this isoenzyme, although the clinical significance of the interaction will depend on the therapeutic window of the affected drug.

Therefore, co-administration of paroxetine 20mg with certain tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), phenothiazine neuroleptics (e.g. perphenazine, thioriadazine) and type 1c antiarrhythmics (flecainide) and metoprolol should be approached with caution and dosage adjustments maybe necessary if these medicines need to be used concurrently.

Pharmacokinetic interactions with tricyclic antidepressants (TCAs) have been reported for all SSRIs. As for other SSRIs, dosing of paroxetine with tricyclic antidepressants is not recommended as TCA plasma levels may be elevated to levels at which there may be an increased risk of TCA related adverse events in some patients which can be serious. Concomitant therapy has not been evaluated for safety and efficacy.

The effects of concomitant administration of paroxetine with neuroleptics and antiarrhythmics have not been studied. Co-administration may lead to pharmacokinetic interactions and therefore should be approached with caution because of the potential increased risk of serious adverse events in some patients e.g. symptoms suggestive of neuroleptic malignant syndrome.

Inhibition of CYP2D6 may decrease plasma concentration of the active tamoxifen metabolite, endoxifen, resulting in reduced therapeutic effect of tamoxifen (see *Warnings and Precautions* section).

Drugs metabolised by cytochrome 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.

Procyclidine

Daily administration of paroxetine increases significantly the plasma levels of procyclidine. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Psychotropic agents

A study of the interaction between paroxetine and diazepam showed no alteration in the pharmacokinetics of paroxetine that would warrant changes in the dose of paroxetine for patients receiving both drugs.

Experience in a limited number of healthy subjects has shown that paroxetine does not increase the sedation and drowsiness associated with haloperiodal, amylobarbitone or oxazepam, when given in combination.

Serotonergic drugs

As with other SSRIs, co-administration with serotonergic drugs (e.g. MAOIs, triptans, tramadol, linezoid, SSRIs, lithium, L-tryptophan which is metabolised to serotonin, buspirone and sumatriptan) may lead to an incidence of 5-HT associated effects (serotonin syndrome). Symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor. The risk of using paroxetine in combination with other CNS active drugs has not been systematically evaluated. Consequently caution is advised if concomitant administration is required.

As with other antidepressants, paroxetine should be used with caution in combination with preparations of St John's Wort (Hypericum perforatum) as increased serotonergic effects may occur.

Lithium

In a study in depressed patients stabilised on lithium, no pharmacokinetic interaction between paroxetine and lithium was observed. However, since there is limited experience in patients, the concurrent administration of paroxetine and lithium should be undertaken with caution.

Pimozide

Concomitant use of paroxetine and pimozide caused an increase in plasma levels and thus may increase the risk of QTc prolongation and/or severe arrythmias such as torsades de pointes.

Alcohol

See *Pharmaceutical Precautions*.

Effects on Laboratory Tests

No information is available.

Overdosage

Overdosage with paroxetine (up to 200 mg) alone and in combination with other drugs has been reported. Events such as coma, convulsions or ECG changes have occasionally been reported. Fatalities have been reported when paroxetine was taken in conjunction with other psychotropic drugs, with or without alcohol or, in isolated cases when taken alone.

As with all overdose attempts, the possibility of multiple drug ingestion should be borne in mind.

Symptoms

Symptoms of overdose with paroxetine include QTc prolongation, Torsades de Pointes, nausea, vomiting, tremor, dilated pupils, fever, blood pressure changes, headache, involuntary muscle contractions, dry mouth, agitation, anxiety, tachycardia and irritability have been reported.

There are no reports of coma or convulsions following overdosage with paroxetine alone.

Treatment

No specific antidote is known. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Where appropriate, the stomach should be emptied by lavage. Following evacuation, 20 to 30g of activated charcoal may be administered every 4 to 6 hours during the first 24 hours after ingestion. Supportive care with frequent monitoring of vital signs and careful observation is indicated.

Pharmaceutical Precautions

Incompatibilities

There are no known incompatilities with Paroxetine tablets. The tablet should be swallowed whole, not chewed.

Shelf Life

36 months from date of manufacture

Storage

Store below 25° C.

Medicine Classification

Prescription Medicine

Package Quantities

Paroxetine 20mg tablets are supplied in carton boxes containing 30 or 60 tablets in either PVC/PE/PVDC/A1 or A1/A1 blisters.

Further Information

Physical and chemical characteristics

Paroxetine mesilate is a white to off-white powder, with a bitter taste and no discernible odour. It has a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents. It is the mesilate salt of a phenylpiperidine compound.

Chemical name: (-)-*trans*-4*R*- (4'-fluorophenyl) - 3*S*- [(3',4'-methylenedioxyphenoxy) methyl]-piperidine methane sulphonate.

Melting point: 143 - 145° C. Solubility: >1000 mg/ml in water.

Molecular formula and weight are $C_{19}H_{20}FNO_3.CH_3SO_3H$ and 425.46 (329.37 as free base), respectively. CAS number: 217797-14-3 for paroxetine mesilate and 61869-08-7 for paroxetine fee base.

Excipients:
Calcium hydrogen phosphate anhydrous, sodium starch glycollate, purified water, magnesium stearate, hypromellose, hydroxypropylecellulose, titanium dioxide, iron oxide yellow (C177492) and iron oxide red (C177491).

Pre-clinical comparisons with paroxetine hydrochloride

Comparative pharmacokinetic studies with paroxetine mesilate and paroxetine hydrochloride hemi-hydrate did not reveal differences between the two salts in absorption, distribution, metabolism and excretion in rates, or in absorption and distribution in pregnant rats. Acute oral and intravenous toxicity studies in mice and rats, repeat dose oral toxicity studies of up to 28 days in rates, and embryofetal development studies in rats did not reveal differences in the toxicity profiles of the two salts.

Clinical Trials

Relapse prevention of depression

A study of depressed outpatients who had responded to paroxetine (Hamilton depression score total <8) during an initial eight week open treatment phase and were then randomised to continuation on paroxetine or placebo for one year demonstrated a significantly lower relapse rate for patients taking paroxetine (15%) compared to those on placebo (39%).

Obsessive compulsive disorder

The effectiveness of paroxetine in the treatment of OCD was demonstrated in two 12 week placebo controlled studies (studies 1 and 2). The results of a third placebo controlled study (study 3) support the effectiveness of paroxetine in the treatment of OCD.

Study 1 was a dose ranging study which originally consisted of 348 patients with OCD and compared placebo, 20mg, 40mg or 60mg daily. Of these 348 patients, 338 had at least one post-baseline efficacy evaluation and were included in the Intent To Treat (ITT) population for efficacy analyses. Paroxetine 40 and 60 mg/day were significantly superior to placebo ($p < 0.001$) in the treatment of OCD as assessed by the primary efficacy variable, mean change from baseline in the Yale-Brown Obsessive Compulsive Disorder (YBOCS) total score. Significant improvement was noted from week 6 onwards.

Studies 2 and 3 were flexible dose studies comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg daily). In Study 2, conducted in 399 patients, 391 had at least one post-baseline efficacy evaluation and were included in the ITT population for efficacy analyses. Paroxetine was significantly more effective than placebo as assessed by the primary efficacy variable mean change from baseline in YBOCS total score ($p = 0.002$). In addition, the efficacy of paroxetine was comparable to that of clomipramine in this study. In Study 3, conducted in 241 patients, 232 had at least one post-baseline efficacy evaluation and were included in the ITT population for efficacy analyses. There was a numerically better response in paroxetine treated patients compared to placebo in the mean change from baseline in YBOCS total score, the magnitude of which was comparable to that in Study 2, though this did not reach statistical significance.

Relapse prevention of obsessive compulsive disorder

A study of OCD outpatients who had responded to paroxetine during an initial six months open treatment phase and were then randomised to continuation on paroxetine or placebo for six months demonstrated a significantly lower relapse for patients taking paroxetine (38%) compared to those on placebo (59%). The risk ratio assessment conducted in this study showed that patients randomised to placebo were 2.7 times more likely to experience a relapse compared to those patients who continued on paroxetine treatment ($p = 0.001$).

Panic disorder

The effectiveness of paroxetine in the treatment of panic disorder was demonstrated in four multicentre, placebo controlled studies of adult outpatients. Patients in all studies had panic disorders (Diagnostic and Statistical Manual, 3rd Edition, DSM III-R) with or without agoraphobia. The studies were conducted over 10-12 weeks. Two of these studies also had an active comparator (clomipramine or alpraxolam) arm. In all four studies, patients received either paroxetine 10 to 60 mg/day (n = 469), clomipramine 10 to 150 mg/day (n = 121), alpraxolam 1 to 6 mg/day (n = 77) or placebo (n = 324). These studies indicated that paroxetine was superior to placebo and comparable with active comparator.

Relapse prevention of panic disorder

The efficacy of paroxetine in preventing relapse of panic disorder was demonstrated in a twelve week double blind prevention study. Patients (n = 43) who were responding during the 10 week double blind phase and a three month double blind extension phase were re-randomised to either paroxetine (10, 20 or 40 mg/day) or placebo. Thirty-three patients treated with paroxetine and 37 patients treated with placebo remained on study at week 12. Patients treated with paroxetine were significantly less likely to relapse than patients receiving placebo (5% versus 30%; p = 0.002).

Benefit in maintenance treatment was demonstrated in a 36 week extension study which compared paroxetine 20 to 60 mg/day (n = 68) to clomipramine 50 to 150 mg/day (n = 63) or placebo (n = 45). Patients who had satisfactorily completed the 12 week double blind phase, continued on the same medication for a further 36 weeks. By week 36, 50 paroxetine patients remained on the study, 43 clomipramine patients and 27 placebo patients remained on study. Maintenance of efficacy of paroxetine was significantly superior to placebo in two out of three primary efficacy variables ($p < 0.05$), and comparable with clomipramine.

Social anxiety disorder/social phobia

The effectiveness of paroxetine in the treatment of social anxiety disorder/social phobia was demonstrated in three 12 week, multicentre, double blind, randomised parallel group, placebo controlled clinical trials (two flexible dose, one dose ranging). Patients received paroxetine 20 to 60 mg/day (n = 522 or placebo (n = 339). These studies indicated that paroxetine was statistically superior to placebo according to either the Liebowitz Social Anxiety Scale (LCAS) or the clinical Global Impression (CGI) scale.

In the fixed dose study, no statistically significant differences in efficacy were observed between the groups treated with 20, 40 and 60 mg/day paroxetine.

Patients in all studies had a primary diagnosis of social anxiety disorder/social phobia according to DSM-IV. A number of exclusion criteria excluded patients from entering the trials e.g. any other AXIS 1 disorder as a primary diagnosis in the last six months.

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