

AUSTRALIAN PRODUCT INFORMATION

PAXTINE®

(paroxetine hydrochloride) film coated tablet



1 NAME OF THE MEDICINE

Paroxetine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PAXTINE tablet contains 20 mg of paroxetine (as hydrochloride) as the active ingredient.

Excipients with known effect: Trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

PAXTINE 20 mg: White, round film-coated tablet marked P/2 and G.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PAXTINE is indicated for the treatment of:

- Major Depression and prevention of relapse of depressive symptoms
- Obsessive Compulsive Disorder (OCD) and prevention of relapse of OCD
- Panic Disorder and prevention of relapse of Panic Disorder
- Social Anxiety Disorder/Social Phobia

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Depression

The recommended dose of PAXTINE is 20 mg (1 tablet) daily. Many patients will respond to a 20 mg daily dose. Patients not responding to a 20 mg dose may benefit from dose increases in 10 mg/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 2 or 3 weeks of initiation of therapy and thereafter as judged clinically appropriate. Dose changes should occur at intervals of at least 1 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 hydrochloride has shown that efficacy was maintained for periods up to one year.

Obsessive Compulsive Disorder

The recommended dose of PAXTINE is 40 mg (2 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.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see Section 5.1 PHARMACODYNAMIC PROPERTIES – 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 (2 tablets). Patients should be started on 10 mg/day and the dose increased weekly in 10 mg increments according to patient's response. Some patients may benefit from having their dose increased up 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.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in two studies, the first a 3-month relapse prevention trial and the second a 36-week extension study (see Section 5.1 PHARMACODYNAMIC PROPERTIES – 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 (1 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.

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 (< 18 years)

PAXTINE is not indicated for use in children or adolescents aged < 18 years. 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use). The safety and efficacy of paroxetine in children aged < 7 years has not been studied.

Use in Renal/Hepatic Impairment

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance < 30 mL/minute) or 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

As with other psychoactive medications, abrupt discontinuation should generally be avoided (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The taper phase regimen used in the clinical trials involved a decrease in the daily dose by 10 mg/day at weekly intervals.

Clinical trials supporting the various approved indications for paroxetine employed a taper phase regimen, rather than an abrupt discontinuation of treatment. The taper phase regimen used in clinical trials involved an incremental 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 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for paroxetine and were at least twice that reported for placebo: abnormal dreams, paraesthesia and dizziness. In the majority of patients, these events were mild and moderate and were self-limiting, and did not require medical intervention.

Also, during paroxetine marketing there have been spontaneous reports of adverse events upon discontinuation (particularly when abrupt), such as dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances, tremor, agitation or anxiety, nausea and sweating. Similar events have been reported for other selective serotonin reuptake inhibitors.

Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which PAXTINE is being prescribed. PAXTINE should not normally be discontinued abruptly. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. It is advised that paroxetine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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.

Prolonged Treatment

The physician who elects to use paroxetine for extended period should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

4.3 CONTRAINDICATIONS

PAXTINE is contraindicated in persons who are known to be hypersensitive to paroxetine or any of its components of the formulation (see Section 6.1 LIST OF EXCIPIENTS).

PAXTINE should not be used in combination with monoamine oxidase (MAO) inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor) and methylthioninium chloride (methylene blue) or within 2 weeks of terminating treatment with MAO inhibitors. Likewise, MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with paroxetine (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

PAXTINE should not be used in combination with thioridazine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

PAXTINE should not be used in combination with pimozide (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical Worsening and Suicide Risk

The risk of suicide attempts is inherent in depression and may persist until significant remission occurs. The risk must be considered in all depressed patients.

Young adults, especially those with Major Depression Disorder (MDD), may be at increased risk for suicidal behaviour during treatment with paroxetine, especially during initial treatment (generally the first one to two months). An analysis of placebo-controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (prospectively defined as aged 18 - 24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25 - 64 years and \geq 65 years), no such increase was observed.

In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]; all of the events were suicide attempts). However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications and this risk may persist until significant remission occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

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 patients presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including the development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of some symptoms, such as agitation, akathisia or mania, could be related either to the underlying disease state or the drug therapy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Akathisia and Mania and Bipolar Disorder and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analysis of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials but there were signals of risk arising from the trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children 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

worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicidal behaviour. 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.

Additionally, patients with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts. All patients should be monitored for clinical worsening (including development of new symptoms) and suicidality throughout treatment, and especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases.

Family and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for PAXTINE should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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.

Monoamine Oxidase Inhibitors (MAOIs)

Treatment with paroxetine should be initiated cautiously at least 2 weeks after terminating treatment with MAO inhibitors (see Section 4.3 CONTRAINDICATIONS) and dosage increased gradually until optimal response is reached.

Diabetes

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

Tricyclic Antidepressants (TCAs)

Caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with paroxetine, because paroxetine may inhibit TCA metabolism via the 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Serotonergic Drugs).

Mania and Bipolar Disorder

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

Tamoxifen

Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). This risk may increase with longer duration of co-administration. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

Bone Fracture

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

Oral Anticoagulants

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Warfarin.

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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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.

Seizure

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 and ECT have not been studied.

Glaucoma

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

Hyponatraemia

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

Cognitive and Motor Performance

Clinical experience has shown that therapy with paroxetine is not associated with the 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.

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.

Bleeding

Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, ecchymoses, haematoma, epistaxis, 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. SSRIs/SNRIs may increase the risk of postpartum haemorrhage. Paroxetine 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 gastroprotection should be considered for high risk patients.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Discontinuation of Treatment

Discontinuation symptoms have been reported with SSRI antidepressants, including paroxetine, when they have been discontinued, particularly when treatment has been stopped abruptly (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). It is, therefore, advised that the dose should be gradually tapered when discontinuing treatment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Symptoms seen on discontinuation of paroxetine treatment in adults:

In clinical 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, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea have been reported. Generally, these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 to 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 Section 4.2 DOSE AND METHOD OF 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 occurred at a rate at least twice that of placebo were: emotional lability, (including suicidal ideation, suicide attempt, mood changes and tearfulness), nervousness, dizziness, nausea and abdominal pain (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Use in Hepatic and Renal Impairment

Caution is recommended in patients with severe renal impairment or in those with hepatic impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the Elderly

Increased plasma concentrations of paroxetine occur in elderly subjects, but the range of concentrations overlap with that observed in younger subjects (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric Use

Paroxetine is not indicated for use in children or adolescents aged < 18 years. 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.

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

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. In clinical trials of paroxetine in children and adolescents, adverse events related to suicidality (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in patients treated with paroxetine compared to those treated with placebo (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The absorption and pharmacokinetics of paroxetine are not affected by food or antacids. Paroxetine has little or no effect on the pharmacokinetics of digoxin, propranolol and warfarin.

Pimozide

Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with paroxetine. This is explained by the known CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant use of pimozide and paroxetine is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Medicines that Interfere with Haemostasis (NSAIDs, aspirin, warfarin etc.)

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence 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 PAXTINE.

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 platelet function, the overall screening tests and the bleeding time were unchanged after paroxetine therapy. Pharmacokinetic analysis has shown that there appears to be no effect of paroxetine on plasma concentrations of either warfarin enantiomer and no difference in warfarin concentrations between paroxetine-dosed and placebo-dosed subjects.

Table 1: INR and bleeding time results in warfarin treated subjects given paroxetine or placebo:

Parameter	n	Paroxetine Mean		Placebo Mean		Paroxetine: Placebo*	95% CI
		Day 1	Day 28	Day 1	Day 28		
INR	21	1.58	1.30	1.50	1.36	0.92	(0.77 - 1.09)
Bleeding time (mins)	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. Co-administration of a single 30 mg dose of paroxetine to subjects receiving chronic daily dosing with 300 mg phenytoin, is associated with decreased paroxetine AUC and half-life of approximately 30% and an increased incidence of adverse events.

When paroxetine is to be co-administered with a known drug metabolising enzyme inhibitor, consideration should be given to using doses at the lower end of the range. No initial dosage adjustment is considered necessary when the drug is to be co-administered with known drug metabolising enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin, sodium valproate). Co-administration of paroxetine with other anticonvulsants may also be associated with an increased incidence of adverse effects. Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

Anticonvulsants (carbamazepine, phenytoin, sodium valproate)

Concomitant administration does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.

Fosamprenavir/ritonavir

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

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 2D6 (CYP2D6). Inhibition of CYP2D6 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 with certain tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), phenothiazines (e.g. perphenazine and promethazine), risperidone, atomoxetine and Type 1C antiarrhythmics (e.g. flecainide) and metoprolol should be approached with caution (dose adjustment of concomitant medicines should be considered).

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 should therefore 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.

Neuromuscular Blockers

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

Thioridazine

Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes and sudden death. As with other drugs which inhibit the hepatic enzyme CYP450 2D6 (including other antidepressants), paroxetine can elevate plasma levels of thioridazine. Therefore, paroxetine should not be administered with thioridazine (see Section 4.3 CONTRAINDICATIONS).

Drugs Metabolised by Cytochrome P450 3A4

An *in vivo* interaction study involving the co-administration under steady state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no significant effect of paroxetine on terfenadine pharmacokinetics. Paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance when it is administered with terfenadine or other drugs that are CYP3A4 substrates.

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 haloperidol, amobarbital or oxazepam, when given in combination.

SSRIs/SNRIs

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Post-marketing Experience).

Serotonergic Drugs

As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5HT associated effects (serotonin syndrome), (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Caution should be advised, and a closer clinical monitoring is required when serotonergic drugs (such as L-tryptophan, triptans, tramadol, SSRIs, lithium, fentanyl and St. John's Wort - *Hypericum perforatum* - preparations) are combined with paroxetine. Concomitant use of paroxetine and MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor) and methylthionium chloride (methylene blue) is contraindicated (see Section 4.3 CONTRAINDICATIONS).

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.

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.

Alcohol

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

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 the reproduction studies in rats at paroxetine doses of 13 mg/kg and above. Vacuolation of epididymal tubular epithelium and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis occurred in male rats at doses of 25 mg/kg/day in toxicity studies.

Use in Pregnancy

Pregnancy category: D

Paroxetine should not be used in pregnancy.

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Discontinuation of Treatment.

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

A retrospective US epidemiological study of 3,581 pregnant 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 ratio 2.20; 95% confidence interval 1.34 - 3.63). There was also an increased risk of cardiovascular malformations for paroxetine compared to other antidepressants (odds ratio 2.08; 95% confidence interval 1.03 - 4.23). 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 the infants of women taking paroxetine and excluding women taking teratogenic drugs as well were 4% (23 cases out of 527 infants) and 2% (11 cases out of 589 infants), respectively. These rates compare with those in the general population of 3% for all congenital malformation and 1% for cardiovascular malformation [Centres for Disease Control and Prevention, USA and Metropolitan Atlanta Birth Congenital Defects Program Data (MACDP)].

A separate study based on the Swedish Medical Birth Register evaluated 4,291 infants born to mothers exposed to SSRIs in early pregnancy. Of these infants, 2.9% were reported to have a congenital malformation, which does not differ from the rate in the unexposed. The rate of congenital malformation in infants whose mothers had been exposed to paroxetine (n = 708) was 3.4%.

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

Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy. 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, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, somnolence and constant crying. In some neonates the complications have resulted in prolonged hospitalisation, respiratory support, and tube feeding. 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 risk of PPHN among infants born to women who used SSRIs late in pregnancy was estimated to be 4 to 5 times higher than the rate of 1 to 2 per 1000 pregnancies observed in the general population.

Reproduction studies performed in rats and rabbits at oral doses of up to 43 and 5 mg/kg, respectively, have revealed no evidence of teratogenic effects. Studies in rats have shown increased pre- and post-implantation losses and decreased postnatal survival at dose levels producing maternal toxicity. Animal reproduction studies are not always predictive of human response.

Use in Lactation

The concentrations of paroxetine detected in the breast milk of lactating women are similar to those in plasma. Neonatal mortality was increased in the offspring of rats receiving oral paroxetine 13 and 43 mg/kg/day during pregnancy and lactation. The risk to the infant by paroxetine administration to lactating women is unknown. Therefore, this drug should not be used by lactating women unless the potential benefit outweighs the possible risk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Cognitive and Motor Performance

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

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% (64/542) 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: very common: $\geq 1/10$, common: $\geq 1/100$ and $< 1/10$, uncommon: $\geq 1/1000$ and $< 1/100$, rare: $\geq 1/10,000$ and $< 1/1000$ and very rare: $< 1/10,000$.

Body as a Whole

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

Uncommon: allergic reaction, chills^{[2][4]}, face oedema, infection^[2], moniliasis, 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: palpitation, vasodilatation, postural hypotension, hypertension, syncope, tachycardia.

Uncommon: bradycardia, conduction abnormalities, abnormal electrocardiogram, hypotension, migraine^[2], ventricular extrasystoles.

Rare: angina pectoris, arrhythmia, atrial arrhythmia, atrial fibrillation, bundle branch block, cerebral ischaemia, cerebrovascular accident, congestive heart failure, extrasystoles, low cardiac output, myocardial infarct, myocardial ischaemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis^[5], thrombosis, varicose vein, vascular headache.

Gastrointestinal

Common: nausea, dry mouth, constipation, diarrhoea, appetite decrease, flatulence, vomiting, oropharynx disorder, dyspepsia, increased appetite; gastrointestinal disorder^[3], tooth disorder^[3], stomatitis^[3].

Uncommon: bruxism, buccal cavity disorders, dysphagia, eructation, gastroenteritis, gastrointestinal flu, glossitis, increased salivation, liver function tests abnormal^[2], mouth ulceration, rectal haemorrhage.

Rare: aphthous stomatitis, bloody diarrhoea, bulimia, colitis, duodenitis, oesophagitis, faecal impaction, faecal incontinence, gastritis, gingivitis^[2], haematemesis, hepatitis, ileus, jaundice, melaena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue oedema, tooth caries, tooth malformation^[5].

Haematological/Lymphatic

Uncommon: anaemia, leukopenia, lymphadenopathy, purpura, white blood cell abnormality.

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

Endocrine

Rare: diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis.

Metabolic/Nutritional

Common: weight gain^{[3][5]}, weight loss^[3], increase in cholesterol levels.

Uncommon: oedema, hyperglycaemia, peripheral oedema, thirst.

Rare: alkaline phosphatase increased^[2], bilirubinaemia, dehydration, gout, hyperphosphataemia^[5], hypocalcaemia, hypoglycaemia, hypokalaemia, hyponatraemia, obesity, AST increased, ALT increased.

Musculoskeletal

Common: myopathy, myalgia, myasthenia.

Uncommon: arthralgia^[2], arthritis, traumatic fracture.

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

Nervous System

Common: somnolence, insomnia, dizziness, tremor, headache, nervousness, anxiety, paraesthesia, libido decreased, agitation, drugged feeling, myoclonus, CNS stimulation, confusion, concentration impaired, depression, emotional lability, vertigo, abnormal dreams (including nightmares), hyperthesia^[2].

Uncommon: abnormal thinking^[2], akinesia, alcohol abuse, amnesia^[2], ataxia, convulsion, depersonalisation^[2], hallucinations, hyperkinesia^[2], hypertonia^[2], incoordination, lack of emotion, manic reaction, paranoid reaction.

Rare: abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, circumoral paraesthesia, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsions, hostility^[2], hyperalgesia, hypokinesia, hysteria, libido increased, manic depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, psychosis, psychotic depression, reflexes increased, restless legs syndrome (RLS), stupor, withdrawal syndrome.

Respiratory

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

Uncommon: asthma, bronchitis, dyspnoea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis^[2].

Rare: emphysema^[5], hiccup, lung fibrosis, pulmonary oedema^[5], sputum increased, voice alteration.

Dermatological

Common: sweating, rash, pruritus, sweat gland disorder^[3].

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

Rare: angioedema, contact dermatitis, erythema nodosum, herpes zoster, hirsutism^[5], maculopapular rash, photosensitivity, skin discolouration, skin ulcer.

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

Special Senses

Common: blurred vision, abnormal vision^[3], taste perversion.

Uncommon: abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, tinnitus^[2], keratoconjunctivitis^[3].

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

Urogenital

Common: abnormal ejaculation^[1], urinary frequency, female/male genital disorder^[1], urination impaired, impotence^[1].

Uncommon: abortion^[1], amenorrhoea^[1], breast pain^[1], cystitis, dysmenorrhoea^{[2][1]}, dysuria, menorrhagia^[1], nocturia, polyuria, urinary incontinence, urinary retention, urinary tract infection^{[2][4]}, urinary urgency, vaginitis^{[2][1]}.

Rare: breast atrophy^[1], female lactation^[1], haematuria, kidney calculus, abnormal kidney function, kidney pain, mastitis^[1], nephritis, oliguria, urethritis, urine abnormality, vaginal moniliasis^[1].

Key to symbols:

[1] = Incidence corrected for gender.

[2] = Adverse experiences reported more frequently in OCD versus depression clinical trials.

[3] = Adverse experiences reported in OCD clinical trials.

[4] = Adverse experiences reported more frequently in Panic versus depression clinical trials.

[5] = Adverse experiences reported in Panic clinical trials.

Post-marketing Experience

Adverse events occurring during post-marketing surveillance:

Blood and Lymphatic System Disorders

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

Very rare: thrombocytopenia.

Immune System Disorders

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

Endocrine Disorders

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

Metabolism and Nutrition Disorders

Common: increases in cholesterol levels, decreased appetite.

Rare: hyponatraemia.

Hyponatraemia has been reported rarely, predominantly in the elderly, and in some cases may be associated with the syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Psychiatric Disorders

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

Uncommon: confusion, hallucinations.

Rare: manic reactions.

These symptoms may be due to the underlying disease.

Nervous System Disorders

Common: dizziness, tremor, headache.

Uncommon: extrapyramidal disorders.

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

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

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

Eye Disorders

Common: blurred vision.

Uncommon: mydriasis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Very rare: acute glaucoma.

Cardiac Disorders

Uncommon: sinus tachycardia.

Vascular Disorders

Uncommon: postural hypotension.

Respiratory, Thoracic and Mediastinal Disorders

Common: yawning.

Gastrointestinal Disorders

Very common: nausea.

Common: constipation, diarrhoea, vomiting, dry mouth.

Very rare: gastrointestinal bleeding.

Hepatobiliary Disorders

Rare: elevation of hepatic enzymes.

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

Elevation of hepatic enzymes has been reported. Post marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice, and/or liver failure) have 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.

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

Renal and Urinary Disorders

Uncommon: urinary retention, urinary incontinence.

Reproductive System and Breast Disorders

Very common: sexual dysfunction.

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

Unknown: Postpartum haemorrhage (this event has been reported for the therapeutic class of SSRIs/SNRIs (see Section 4.4 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – SSRIs/SNRIs).

General Disorders and Administration Site Conditions

Common: asthenia, body weight gain.

Very rare: peripheral oedema.

Discontinuation Symptoms

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

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

As with many psychoactive medicines, discontinuation of paroxetine (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), tremor, agitation or anxiety, nausea, headache, confusion, diarrhoea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adverse Events from Paediatric Clinical Trials

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

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

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose with paroxetine (up to 2000 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

Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), sedation, blood pressure changes, involuntary muscle contractions and facial flush have been reported.

Treatment

No specific antidote is known. Treatment should consist of those general measures employed in the management of overdose with any antidepressant.

Supportive care with frequent monitoring of vital signs and careful observation is indicated. Patient management should be as clinically indicated, or as recommended by the national poisons centre, where available.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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, is thought to be related to its specific inhibition of 5HT uptake in brain neurones.

In vitro studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for α_1 -, α_2 - and β -adrenoreceptors, dopamine (D_2), 5HT₁-like, 5HT₂ and histamine (H_1) receptors. This lack of interaction with postsynaptic receptors *in vitro* is substantiated by *in vivo* studies which 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 1/50 of the parent compound, it is most unlikely that they contribute to paroxetine's therapeutic effect.

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 electroencephalographic (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. 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 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, in addition to its significant antidepressant effects, can improve associated symptoms of anxiety.

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 Obsessive Compulsive Disorder (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, 20 mg, 40 mg or 60 mg 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 mg 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 Intent to Treat (ITT) population for efficacy analyses. Paroxetine was significantly more effective than placebo as assessed by the primary efficacy variables 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 Intent to Treat (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 6-month open treatment phase and were then randomised to continuation on paroxetine or placebo for 6 months, demonstrated a significantly lower relapse rate 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 Disorder (Diagnostic and Statistical Manual, 3rd Edition, DSM III-R) with or without agoraphobia. The studies were conducted over 10 to 12 weeks. Two of these studies also had an active comparator (clomipramine or alprazolam) arm.

In all four studies, patients received either paroxetine 10 to 60 mg/day (n = 469), clomipramine 10 to 150 mg/day (n = 121), alprazolam 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 12-week double-blind relapse prevention study. Patients (n = 43) who were responders during the 10-week double-blind phase and a 3-month double-blind extension phase were re-randomised to either paroxetine (10, 20, or 40 mg/day) or placebo. 33 paroxetine treated patients treated with paroxetine and 37 placebo treated patients 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 (2 flexible dose, 1 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 (LSAS) 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 6 months.

5.2 PHARMACOKINETIC PROPERTIES

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 non-linear kinetics. These properties are a consequence of the fact that one of the enzymes that metabolises paroxetine is the readily saturable cytochrome P450 enzyme 2D6 (CYP2D6). However, because this enzyme becomes saturated early on following commencement of paroxetine treatment, the non-linearity observed during a subsequent dose increase is generally small and is confined to those subjects who achieve low plasma levels at low doses.

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 sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 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 achieved between individuals. However, no correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy). 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.

The elimination half-life is variable but is generally about 1 day. However, because of the reduction in plasma clearance which occurs on multiple dosing (non-linear kinetics: see Section 5.2 PHARMACOKINETIC PROPERTIES – Absorption). Seven to fourteen days are required for the achievement of steady state. Thereafter, pharmacokinetics do not appear to change during long-term therapy. Considerable variation can occur in the plasma concentrations achieved between individuals, possibly due to variable first-pass effect and variability in clearance.

A bioequivalence study comparing PAXTINE, and the brand leader Aropax® tablets, in thirty-six young adult volunteers showed that there was no statistically significant difference between the two formulations with respect to the rate or extent of absorption of paroxetine. The results for the 90% CI for the ratio of mean C_{max} values was 0.978 to 1.117, whilst the 90% CI for the ratio of AUC_{0-t} was 1.000 to 1.139. These results for the two formulations were within the bioequivalence acceptance limits.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following excipients: calcium hydrogen phosphate, colloidal anhydrous silica, magnesium stearate, methacrylic acid copolymer, purified talc, sodium starch glycollate and titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack (PVC/PVDC)

Pack size: 30 tablets

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 227120 - PAXTINE paroxetine 20mg (as hydrochloride) tablet blister pack

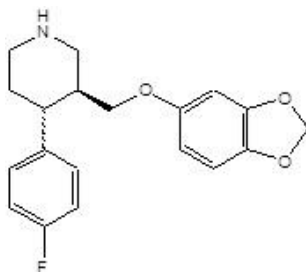
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Paroxetine hydrochloride anhydrous is a white to off-white crystalline powder, with a melting point of 118°C to 120.5°C, and solubility of 6.53 mg/mL in water. Paroxetine is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents.



Chemical name: (3S,4R)-(-)-4-(4'-Fluorophenyl)-3-[3',4'-(methylenedioxy)-phenoxy]methylpiperidine hydrochloride

Molecular formula: C₁₉H₂₀FNO₃.HCl

Molecular weight: 365.83

CAS Number

78246-49-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR**Alphapharm Pty Ltd trading as Viatris**

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9 DATE OF FIRST APPROVAL

24/10/2014

10 DATE OF REVISION

24/03/2026

Summary Table of Changes

Section Changed	Summary of New Information
4.2, 4.6	Minor editorial change

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