

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

AROPAX paroxetine 20 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 22.8 mg of paroxetine hydrochloride hemihydrate equivalent to 20 mg of paroxetine free base.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Film coated tablet

White, film coated, oval shaped biconvex tablets de-bossed with "20" on one side and a break bar on the other to enable the tablets to be broken in half if required.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults aged 18 years and older

Major Depressive Disorder:

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

AROPAX is indicated for the prevention of relapse and also recurrence of further depressive episodes (see section 5 Pharmacological Properties).

Obsessive Compulsive Disorder:

AROPAX is indicated for the treatment of Obsessive Compulsive Disorder (OCD) (see section 5 Pharmacological Properties).

Panic Disorder:

AROPAX is indicated for the treatment of Panic Disorder with and without agoraphobia (see section 5 Pharmacological Properties).

Social Anxiety Disorder/Social Phobia:

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

Generalised Anxiety Disorder:

AROPAX has been shown to be effective in the treatment of Generalised Anxiety Disorder (see section 5 Pharmacological Properties).

Post-Traumatic Stress Disorder:

AROPAX has been shown to be effective in the treatment of Post-Traumatic Stress Disorder.

Children and adolescents (<18 years)

AROPAX is not indicated for use in children or adolescents aged <18 years (see section 4.4 Special warnings and precautions for use).

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy, and do not support the use of AROPAX in the treatment of depression in this population (see section 4.4 Special warnings and precautions for use).

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

4.2 Dose and method of administration

Dose

Use in Adults

Major Depressive Disorder:

The recommended dose is 20 mg daily. Some 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. It is recommended that AROPAX is administered once daily with food. Based on observed beneficial effects on sleep it is recommended that the dose be taken in the morning. If, however, a patient experiences unacceptable daytime somnolence with AROPAX, consideration should be given to dosing at bedtime. The tablet should be swallowed rather than chewed.

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

Patients with depression should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months.

Obsessive Compulsive Disorder:

The recommended dose 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.

It is recommended that AROPAX is administered once daily with food. The tablet should be swallowed rather than chewed.

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

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 patient's response. Some patients may benefit from having their dose increased up to a maximum of 60 mg/day.

A low initial starting dose is recommended to minimise the potential worsening of panic symptomatology, which is generally recognised to occur early in the treatment of this disorder.

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

Social Anxiety Disorder/Social Phobia:

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

Generalised Anxiety Disorder:

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

Post-Traumatic Stress Disorder:

For the majority of patients, the recommended starting and maintenance dose is 20 mg daily. However, some patients not responding to a 20 mg dose may benefit from having dose increases in 10 mg increments as required, up to a maximum of 50 mg/day according to the patient's response.

The use of AROPAX beyond 12 weeks has not been investigated in clinical trials.

Discontinuation of AROPAX:

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 Undesirable effects). 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.

Special Populations*Elderly population*

Increased plasma concentrations of AROPAX occur in elderly subjects, but the range of concentrations overlaps with that observed in younger subjects.

Renal/Hepatic Impairment

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

Paediatric population

AROPAX is not indicated for use in children or adolescents aged <18 years (see section 4.1 Therapeutic indications and section 4.4 Special warnings and precautions for use).

Method of administration

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

The 20 mg tablets have functional break lines to allow for breaking the tablets in half to yield 10 mg dose if needed.

4.3 Contraindications

Known hypersensitivity to paroxetine and excipients.

Paroxetine should not be used in combination with monoamine oxidase (MAO) inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylnthioninium chloride (methylene blue)) or within two weeks of terminating treatment with MAO inhibitors. Likewise, MAO inhibitors should not be introduced within two weeks of cessation of therapy with paroxetine (see section 4.5 Interaction with other medicines and other forms of interaction).

Paroxetine should not be used in patients receiving medications that can prolong QT interval and are also metabolised by CYP450 2D6, such as thioridazine or pimozide (see section 4.5 Interaction with other medicines and other forms of interaction).

4.4 Special warnings and precautions for use

Children and Adolescents (<18 years):

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders. In clinical trials of AROPAX 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 AROPAX compared to those treated with placebo (see section 4.8 Undesirable effects). Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Clinical worsening and suicide risk in adults:

Young adults, especially those with MDD, may be at increased risk for suicidal behaviour during treatment with paroxetine. An analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (prospectively defined as aged 18 to 24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25 to

64 years and ≥ 65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]; all of the events were suicide attempts). However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18 to 30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

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

Other psychiatric conditions for which paroxetine is prescribed can be associated with an increased risk of suicidal behaviour, and these conditions may be co-morbid with MDD.

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

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. It should be recognised that the onset of some symptoms, such as agitation, akathisia or mania, could be related either to the underlying disease state or the drug therapy (see Akathisia and Mania and Bipolar Disorder below and section 4.8 Undesirable effects).

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Akathisia:

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

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. Examples of serotonergic drugs include monoamine oxidase inhibitors (see section 4.3) and other serotonergic agents such as opioids for example pethidine, tramadol, dextromethorphan. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine and/or the interacting medicine, should be discontinued or reduced depending on severity of symptoms, 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 4.3 Contraindications and section 4.5 Interaction with other medicines and other forms of interaction).

Mania and Bipolar disorder:

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that 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 Interaction with other medicines and other forms of interaction). 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.

MAO Inhibitors:

Treatment with paroxetine should be initiated cautiously at least two weeks after terminating treatment with MAO inhibitors and dosage of paroxetine should be

increased gradually until optimal response is reached (see section 4.3 Contraindications and section 4.5 Interaction with other medicines and other forms of interaction).

Cardiac Conditions:

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

QT Prolongation:

Cases of QT interval prolongation have been reported, although causality with paroxetine has not been established.

Paroxetine should be used with caution in patients with a history of QT interval prolongation, patients taking anti-arrhythmic or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease.

For further information, see section 4.3 Contraindications and section 4.5 Interaction with other medicines and other forms of interaction.

Epilepsy:

As with other antidepressants, paroxetine should be used with caution in patients with epilepsy.

Seizures:

Overall the incidence of seizures is less than 0.1% in patients treated with paroxetine.

Paroxetine should be discontinued in any patient who develops seizures.

Electroconvulsive Therapy (ECT):

There is little clinical experience of the concurrent administration of paroxetine with ECT.

Glaucoma:

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

Renal/hepatic 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).

Hyponatraemia:

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

Haemorrhage:

Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, haematoma, epistaxis, gynaecological 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. Aropax 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 (see section 4.8 Undesirable effects). Pharmacological gastroprotection should be considered for high risk patients. SSRIs may increase the risk of postpartum haemorrhage (see section 4.6 Fertility, pregnancy and lactation).

QTc prolongation/Torsades de Pointes:

Cases of QTc prolongation and Torsades de Pointes (TdP), have been reported during the post-marketing use of paroxetine although a causal relationship with drug therapy has not been established. 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 section 4.5 Interaction with other medicines and other forms of interaction). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

In high risk patients (e.g. congenital long QT syndrome or multiple risk factors), an ECG should be performed prior to starting treatment, at steady state, after dose increases or 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 (e.g. 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.

Reversible cerebral vasoconstriction syndrome:

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been reported with use of serotonergic agents such as SSRIs or triptans.

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 two weeks, though in some individuals they may be prolonged (two to three months or more). It is therefore advised that paroxetine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Discontinuation of Paroxetine" in section 4.2 Dose and method of administration).

Sexual dysfunction:

SSRIs may cause symptoms of sexual dysfunction (see section 4.8 Undesirable effects). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

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 Undesirable effects).

Alcohol:

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

4.5 Interaction with other medicines and other forms of interaction

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: the concomitant use of paroxetine and alcohol is not advised.

Serotonergic drugs

As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5-HT associated effects (see "Serotonin syndrome" in 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, SSRIs, lithium, St. John's Wort – *Hypericum perforatum* – preparations and

opioids for example pethidine, dextromethorphan, tramadol, fentanyl) are combined with paroxetine.

Concomitant use of paroxetine and MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)) is contraindicated (see section 4.3 Contraindications).

Pimozide

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

Drug metabolising enzymes

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolising enzymes.

When paroxetine is to be co-administered with a known drug metabolising enzyme inhibitor, consideration should be given to using doses at the lower end of the range.

No initial dosage adjustment is considered necessary when the drug is to be co-administered with known drug metabolising enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin). Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

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

Procyclidine: Daily administration of paroxetine increases significantly the plasma levels of procyclidine. If anti-cholinergic effects are seen, the dose of procyclidine should be reduced.

Anticonvulsants: carbamazepine, phenytoin, sodium valproate. Concomitant administration does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.

Neuromuscular blockers:

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

CYP2D6 inhibitory potency of paroxetine:

As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered drugs metabolised by this enzyme. These include certain tricyclic antidepressants (e.g. amitriptyline, nortriptyline, imipramine and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine, see section 4.3 Contraindications), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol.

Tamoxifen has an important active metabolite, endoxifen, which is produced by CYP2D6 and contributes significantly to the efficacy of tamoxifen. Irreversible inhibition of CYP2D6 by paroxetine leads to reduced plasma concentrations of endoxifen (see section 4.4 Special warnings and precautions for use).

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.

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 AROPAX.

Medicines that prolong the QT interval:

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. Torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval (see "QTc prolongation and Torsades de Pointes" in section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Pregnancy

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 section 4.2 Dose and method of administration - Discontinuation of Paroxetine and section 4.4 Special warnings and precautions for use – 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 ratio 1.8; 95% confidence interval 1.2 – 2.8). There was also an increased risk of cardiovascular malformations for paroxetine compared to other antidepressants (odds ratio 1.5; 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 SSRIs 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, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and somnolence. In some instances the reported symptoms were described as neonatal withdrawal symptoms. In a majority of instances the complications were reported to have arisen either immediately or soon (<24 hours) after delivery.

Epidemiological studies have shown that the use of SSRIs (including paroxetine) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The increased risk among infants born to women who used SSRIs late in pregnancy was reported to be four to five times higher than observed in the general population (rate of one to two per 1000 pregnancies).

Animal studies have not shown any teratogenic or selective embryotoxic effects. 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. Paroxetine should not be used during pregnancy unless the potential benefit outweighs the possible risk.

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

Breast-feeding

Small amounts of paroxetine are excreted into breast milk. In published studies, serum concentrations in breast-fed infants were undetectable (<2 nanograms/ml) or very low (<4 nanograms/mL). 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.

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.

4.7 Effects on ability to drive and use machines

Clinical experience has shown that therapy with paroxetine is not associated with impairment of cognitive or psychomotor function. However, as with all psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

4.8 Undesirable effects

Summary of adverse reactions

Some of the adverse experiences listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy. Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$, $<1/10$), uncommon ($\geq 1/1,000$, $<1/100$), rare ($\geq 1/10,000$, $<1/1,000$), very rare ($<1/10,000$), including isolated reports. The frequencies of common and uncommon events were generally determined from pooled safety data from a clinical trial population of >8000 paroxetine-treated patients and are quoted as excess incidence over placebo. Rare and very rare events were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

Blood & lymphatic system disorders

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes (including purpura, haematomas, and very rarely epistaxis, gynaecological bleeding and gastrointestinal bleeding).

Very rare: thrombocytopenia.

Immune system disorders

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

Endocrine disorders

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

Metabolism & nutrition disorders

Common: increases in cholesterol levels, decreased appetite.

Rare: hyponatraemia.

Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Psychiatric disorders

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

Uncommon: confusion, hallucinations.

Rare: manic reactions, depersonalisation, panic attacks.

These symptoms may be due to the underlying disease.

Nervous system disorders

Common: dizziness, tremor, headache.

Uncommon: extrapyramidal disorders.

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

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

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

Eye disorders

Common: blurred vision.

Uncommon: mydriasis (see Warnings and Precautions).

Very rare: acute glaucoma.

Cardiac disorders

Uncommon: sinus tachycardia

Rare: QTc prolongation (including Torsades de Pointes)*, bradycardia.

* 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.

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

Common: yawning

Gastrointestinal disorders

Very common: nausea.

Common: constipation, diarrhoea, vomiting, dry mouth.

Very rare: gastrointestinal bleeding.

Hepato-biliary disorders

Rare: elevation of hepatic enzymes.

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

Elevation of hepatic enzymes has been reported. Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice, and/or liver failure) have also been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

Skin & subcutaneous tissue disorders

Common: sweating.

Uncommon: skin rashes, pruritis.

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

Renal & urinary disorders

Uncommon: urinary retention, urinary incontinence.

Reproductive system & breast disorders

Very common: sexual dysfunction.

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

Very rare: priapism.

General disorders & administration site conditions

Common: asthenia, body weight gain.

Very rare: peripheral oedema.

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia.

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and tricyclic antidepressants. The mechanism leading to this risk is unknown.

Symptoms seen on discontinuation of paroxetine treatment

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

Uncommon: agitation, nausea, tremor, confusion, sweating, diarrhoea, visual disturbances, palpitations.

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), agitation or anxiety, nausea, headache, tremor, confusion, diarrhoea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when 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).

Paediatric population

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 (see section 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms and Signs:

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

Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under "Adverse effects", fever, blood pressure changes, involuntary muscle contractions, anxiety and tachycardia have been reported.

Patients have generally recovered without serious sequelae. Events such as coma or ECG changes (including QT prolongation and Torsades de Pointes) have occasionally been reported and, very rarely a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic drugs, with or without alcohol.

Treatment:

No specific antidote is known.

The treatment should consist of those general measures employed in the management of overdose with any antidepressant.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake and its antidepressant action and effectiveness in the treatment of OCD and Panic Disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

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

Paroxetine has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties.

In accordance with this selective action, *in vitro* studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for alpha₁, alpha₂ and beta-adrenoceptors, dopamine (D₂), 5-HT₁ like, 5-HT₂ and histamine (H₁) receptors. This lack of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies, which demonstrate lack of CNS depressant and hypotensive properties.

Pharmacodynamic effects

Paroxetine does not impair psychomotor function and does not potentiate the depressant effects of ethanol.

As with other selective 5-HT uptake inhibitors, paroxetine causes symptoms of excessive 5-HT receptor stimulation when administered to animals previously given monoamine oxidase (MAO) inhibitors or tryptophan.

Behavioural and EEG studies indicate that paroxetine is weakly activating at doses generally above those required to inhibit 5-HT uptake. The activating properties are not "amphetamine-like" in nature.

Animal studies indicate that paroxetine is well tolerated by the cardiovascular system.

Paroxetine produces no clinically significant changes in blood pressure, heart rate and ECG after administration to healthy subjects.

Studies indicate that, in contrast to antidepressants, which inhibit the uptake of nor-adrenaline, paroxetine has a much reduced propensity to inhibit the antihypertensive effects of guanethidine.

5.2 Pharmacokinetic properties

Absorption

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

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

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

Distribution

Paroxetine is extensively distributed into tissues and pharmacokinetic calculations indicate that only 1% of the paroxetine in the body resides in the plasma.

Approximately 95% of the paroxetine present in the plasma is protein bound at therapeutic concentrations.

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

Biotransformation

The principal metabolites of paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to paroxetine's therapeutic effects.

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

Elimination

About 64% of the dose is excreted in the urine; urinary excretion of unchanged paroxetine is generally less than 2% of the 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 one day.

Special populations

Elderly and Renal/Hepatic Impairment

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.

Other

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

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

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

The combination of AROPAX 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 AROPAX in the treatment of Panic Disorder has been maintained for up to one year.

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

5.3 Preclinical safety data

Toxicology studies have been conducted in rhesus monkeys and albino rats; in both, the metabolic pathway is similar to that described for humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to one year duration at doses that were six times higher than the recommended range of clinical doses.

Carcinogenesis:

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

Genotoxicity:

Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Starch Glycollate

Magnesium Stearate

Calcium hydrogen phosphate dehydrate

Titanium dioxide

Hypromellose

Macrogol 400

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

Store in a dry place at a temperature not exceeding 30°C.

6.5 Nature and contents of container

Child-resistant blister packs comprising opaque polyvinyl chloride (PVC) backed with aluminium foil laminated with paper containing 30 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited

Private Bag 106600

Downtown

Auckland

NEW ZEALAND

Phone: (09) 367 2900

Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
30 April 1992

10. DATE OF REVISION OF THE TEXT

29 May 2024

Summary table of changes:

Section changed	Summary of new information
4.4	Addition of warning information for alcohol use
4.5	Revision of warning information for alcohol
4.7	Revision of information regarding concomitant use of paroxetine and alcohol
4.9	Revision of information regarding patient adverse effect recovery

Version 19.0

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