



New Zealand Data Sheet

Apo-Paroxetine Paroxetine Hydrochloride 20mg

Presentation

White, oval-shaped, biconvex, film-coated tablet. Partial bisect and engraved "20" on one side, other side plain. Each tablet is approximately 11.5mm long by 6.3mm wide and typically weighs 237mg.

Uses

Actions

Paroxetine is a potent and selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI). This activity of the drug on brain neurons is thought to be responsible for its antidepressant effects.

Paroxetine is a phenylpiperidine derivative, which is chemically unrelated to the tricyclic or tetracyclic or other available antidepressants. In receptor binding studies, paroxetine did not exhibit significant affinity for the adrenergic (alpha-1, alpha-2 and beta), dopaminergic, serotonergic (5HT1, 5HT2), or histaminergic receptors of rat brain membrane. 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.

A weak affinity for the muscarinic acetylcholine receptor was evident.

The predominant metabolites of paroxetine are essentially inactive as 5-HT reuptake inhibitors. These metabolites are polar and conjugated products of oxidation and methylation which are readily cleared.

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

Pharmacokinetics

Paroxetine is well absorbed after oral administration and undergoes first-pass metabolism. In healthy volunteers, the presence of, or absence of food did not appreciably affect the absorption of a single 30mg oral dose of paroxetine. Owing to the extensive distribution of paroxetine into



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the tissues, less than 1% of the total drug in the body is believed to reside in the systemic circulation.

Paroxetine is subject to a biphasic process of metabolic elimination which involves presystemic (first-pass) and systemic pathways. First-pass metabolism is extensive, but may be partially saturable, accounting for the increased bioavailability observed with multiple dosing. The metabolism of paroxetine is accomplished in part by cytochrome P450(2D6). Saturation of the enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see warnings and precautions). The majority of the dose appears to be oxidised to a catechol intermediate which is converted to highly polar glucuronide and sulphate metabolites through methylation and conjugation reactions. The glucuronide and sulphate conjugates of paroxetine are about >10,000 and 3,000 times less potent, respectively, than the parent compound as inhibitors of 5-HT reuptake in rat brain synaptosomes. About 64% of an administered dose of paroxetine is excreted in 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 bile; faecal excretion of unchanged paroxetine represents less than 1% of the dose. Thus paroxetine is eliminated almost entirely by metabolism.

A wide range of interindividual variation is observed for the pharmacokinetics parameters. Following the single or multiple dose administration of paroxetine 20-50mg, the mean elimination half-life value is about 24 hours, although a range of 3 to 65 hours has been reported. Both the rate of absorption and the terminal elimination half-life appear to be independent of dose.

Steady-state plasma concentrations of paroxetine are generally achieved in 7 to 14 days, and pharmacokinetics do not appear to change during long-term therapy.

No correlation has been established between paroxetine plasma concentrations and therapeutic efficacy or the incidence of adverse reactions.

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 plasma is protein bound at therapeutic concentrations. After the administration of a single 50mg oral dose to lactating women, the concentrations of the paroxetine detected in breast milk were similar to those in plasma.

Indications

Adults

Depression:

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

APO-PAROXETINE is indicated for the prevention of relapse and also recurrence of further depressive episodes.

In the treatment of depressive disorders, APO-PAROXETINE exhibits comparable efficacy to standard antidepressants.

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



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APO-PAROXETINE, in addition to its significant antidepressant effects, also improves associated symptoms of anxiety.

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

Morning dosing with APO-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 APO-PAROXETINE therapy.

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

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

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

Obsessive Compulsive Disorder:

APO-PAROXETINE is indicated for the treatment of Obsessive Compulsive Disorder (OCD).

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

Panic Disorder:

APO-PAROXETINE is indicated for the treatment of Panic Disorder with and without agoraphobia.

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

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

Social Anxiety Disorder/Social Phobia:

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

Generalised Anxiety Disorder:

APO-PAROXETINE has been shown to be effective in the treatment of Generalised Anxiety Disorder.

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

Posttraumatic Stress Disorder:

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



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ALL INDICATIONS

Children and adolescents (<18 years)

APO-PAROXETINE is not indicated for use in children or adolescents aged <18 years (see Warnings and Precautions).

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy, and do not support the use of APO-PAROXETINE in the treatment of depression in this population (see Warnings and Precautions).

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

Dosage and Administration

APO-PAROXETINE should be administered once daily with food, preferably in the morning. The tablet(s) should be swallowed rather than chewed.

Depression:

The recommended dose is 20mg/day. If a patient is not responding the dosage can be increase by 10mg/day in weekly increments up to a maximum of 50mg/day. The dosage should be reviewed and adjusted within 2 to 3 weeks of initiation of therapy and thereafter as deemed clinically appropriate. Any changes in dosage should occur at intervals of at least one week.

Obsessive Compulsive Disorder (OCD):

The recommended dose is 40mg/day. Patients should start on an initial dose of 20mg/day and the dose can then be increased in weekly 10mg/day increments. Doses up to a maximum of 60mg/day may benefit some patients.

Panic Disorder:

The recommended dose is 40mg/day. Patients should begin treatment at a dose of 10mg/day with the dose being adjusted in weekly 10mg/day increments according to their individual response. Doses up to a maximum of 60mg/day may benefit some patients.

Social Anxiety Disorder/ Social Phobia:

The recommended dose is 20mg/day. If a patient is not responding the dosage can be increase by 10mg/day in weekly increments up to a maximum of 50mg/day.

It is generally recommended that a course of antidepressant drug treatment should continue for a sufficient period to ensure the patient is free from symptoms. This period may be several months for depression but can be longer for OCD and Panic Disorder.

Generalised Anxiety Disorder:

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

Posttraumatic Stress Disorder:

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



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The use of APO-PAROXETINE beyond 12 weeks has not been investigated in clinical trials.

Use in Elderly:

Increased plasma concentrations of paroxetine occur in elderly subject, but the range of concentrations overlaps those observed in younger subjects. Dosing should begin with the adult starting dose and may be increased by weekly 10mg/day increments up to 40mg/day, according to the patients response.

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

APO-PAROXETINE should not be used in patients under 18 years of age (see 'Warnings and Precautions').

Renal/Hepatic Impairment:

Increased plasma concentrations of paroxetine occur in patients with renal impairments (creatinine clearance < 30ml/min) or severe hepatic impairment. Dosages should be restricted to the lower end of the dosage range.

Discontinuation of Apo-Paroxetine

As with other psychoactive medications, abrupt discontinuation should generally be avoided (see Warnings and Adverse Reactions sections). 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.

Contraindications

APO-PAROXETINE is contraindicated in patients with a known hypersensitivity to paroxetine or any of its excipients.

APO-PAROXETINE is also contraindicated in patients taking monoamine oxidase inhibitors (MAO) (see Warnings and Precautions).

Paroxetine should not be used in combination with thioridazine, because, as with other drugs, which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine (see Interactions). Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.

Paroxetine should not be used in combination with pimozide

Warnings and Precautions

Children and Adolescents (under 18 years of age):

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 APO-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 APO-PAROXETINE compared to those treated with placebo (see Adverse Reactions). Long-



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term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Clinical Worsening and Suicide Risk:

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

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

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, and should receive careful monitoring during treatment.

Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

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

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

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.

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

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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 Contraindications and Interactions).

Mania and Bipolar Disorder:

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that paroxetine is not approved for use in treating bipolar depression.

MAO Inhibitors:

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

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 Interactions section). This risk may increase with longer duration of co-administration. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

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.

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 Dosage and 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, 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. Apo-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.



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Cardiac Conditions:

Paroxetine does not generally produce clinically significant changes in blood pressure, heart rate or ECG. APO-PAROXETINE has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Hence, the usual precautions should be observed in such patients. Like other SSRI's, paroxetine infrequently causes mydriasis and therefore should be used with caution in patients with narrow angle glaucoma.

Information for Patients and Families:

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

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 and electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea have been reported. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that paroxetine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Discontinuation of Paroxetine", Dosage and Administration).

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 Adverse Effects).

Use in Pregnancy and Lactation

Category C

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

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



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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, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and somnolence. In some instances the reported symptoms were described as neonatal withdrawal symptoms. In a majority of instances the complications were reported to have arisen either immediately or soon (<24 hours) after delivery.

Epidemiological studies have shown that the use of SSRIs (including paroxetine) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The increased risk among infants born to women who used SSRIs late in pregnancy was reported to be 4 to 5 times higher than observed in the general population, (rate of 1 to 2 per 1000 pregnancies)

Animal studies have not shown any teratogenic or selective embryotoxic effects. There have been reports of premature birth in pregnant women exposed to paroxetine or others SSRIs, although a causal relationship with drug therapy has not been established. Paroxetine should not be used during pregnancy unless the potential benefit outweighs the possible risk.

Small amounts of paroxetine are excreted into breast milk. In published studies, serum concentrations in breast-fed infants were undetectable (<2 ng/ml) or very low (<4 ng/ml). No signs of drug effects were observed in these infants. Nevertheless, paroxetine should not be used during lactation unless the expected benefits to the mother justify the potential risks for the infant.



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Effect on ability to drive or operate machinery

Although paroxetine did not cause sedation or interfere with psychomotor performance in placebo-controlled studies in normal subjects, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that APO-PAROXETINE does not affect them adversely.

Other: Preclinical Safety Data

Toxicology studies have been conducted in rhesus monkeys and albino rats; in both, the metabolic pathway is similar to that described for humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to one year duration at doses that were 6 times higher than the recommended range of clinical doses.

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

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

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

Adverse Effects

In clinical trials the most commonly observed adverse effects from the use of paroxetine were: asthenia, constipation, decreased appetite, diarrhea, dizziness, dry mouth, insomnia, male sexual dysfunction, nausea, somnolence, sweating and tremor.

Twenty-one percent of over 4000 patients who received paroxetine in worldwide clinical trials in depression discontinued treatment due to an adverse experience. The most common events leading to discontinuation (reported by 1% or more of subjects) included: agitation, asthenia, constipation, dizziness, headache, insomnia, male sexual dysfunction, nausea, somnolence and tremor. Following discontinuation of treatment some patients may experience physical symptoms such as: agitation/restlessness, dizziness/lightheadedness, gastrointestinal complaints, headache and sleep disturbance. These events are usually mild and transient.

The following adverse effects have been reported rarely: dizziness, rash, acute glaucoma, urinary retention, peripheral and facial edema, sinus tachycardia, thrombocytopenia, serotonergic syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), symptoms suggestive of hyperprolactinaemia/galactorrhoea and hyponatraemia (predominantly in the elderly).

Elevation of hepatic enzymes has been reported. Serious liver abnormalities have been reported rarely. If there is a prolonged elevation on liver function test, discontinuation of treatment with paroxetine should be considered.

As with other SSRI's, transient increase or decreases in blood pressure have been reported following treatment with paroxetine, usually in patients with preexisting hypertension or anxiety. Also as with other SSRI's, confusion, convulsions and photosensitivity reactions have been reported rarely.



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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, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Immune system disorders

Very rare: allergic reactions (including urticaria and angioedema).

Endocrine disorders

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

Metabolism & nutrition disorders

Common: 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.

Uncommon: confusion, hallucinations.

Rare: manic reactions.

These symptoms may be due to the underlying disease.

Nervous system disorders

Common: dizziness, tremor.

Uncommon: extrapyramidal disorders.

Rare: convulsions, akathisia.

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

Vascular disorders

Uncommon: transient increases or decreases in blood pressure.

Transient increases or decreases of blood pressure have been reported following treatment with paroxetine, usually in patients with pre-existing hypertension or anxiety.

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Respiratory, thoracic and mediastinal disorders

Common: yawning.

Gastrointestinal disorders

Very common: nausea.

Common: constipation, diarrhoea, 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.

Very rare: photosensitivity reactions.

Renal & urinary disorders

Uncommon: urinary retention, urinary incontinence.

Reproductive system & breast disorders

Very common: sexual dysfunction.

Rare: hyperprolactinaemia / galactorrhoea.

General disorders & administration site conditions

Common: asthenia.

Very rare: peripheral oedema.

Symptoms seen on discontinuation of paroxetine treatment

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), 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 Dosage and Administration & Warnings and Precautions).

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

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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

Interactions

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.

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 a medicines concurrently with Apo-Paroxetine.

Drugs metabolised by P450 isoenzymes:

CYP2D6: Like other selective serotonin reuptake inhibitors, paroxetine inhibits the specific hepatic cytochrome P450 isoenzyme (CYP2D6) which is responsible for the metabolism of debrisoquine and sparteine. Inhibition of CYP2D6 may increase plasma levels of co-administered medicines such as tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), selective serotonin reuptake inhibitors (e.g. fluoxetine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine), risperidone, type 1c antiarrhythmics (e.g. propafenone and flecainide) And metoprolol. Dosage adjustments may be necessary if these medicines need to be used concurrently.

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

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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. Concurrent administration of paroxetine with terfenadine and other drugs that are CYP3A4 substrates would not be expected to cause a hazard.

Tryptophan:

Tryptophan can be metabolised to serotonin. Adverse effects (e.g. headache, nausea, sweating and dizziness) have been reported when tryptophan was administered with another selective 5-HT reuptake inhibitor. Therefore, paroxetine should not be used in combination with tryptophan.

Lithium:

In a study of 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 APO-PAROXETINE and lithium should be undertaken with caution.

Alcohol:

The concomitant use of paroxetine and alcohol is not advised even though paroxetine does not increase the impairment of mental and motor skills caused by alcohol.

Microsomal Enzyme Inhibition/Induction:

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolising enzymes. Steady state levels of paroxetine (30mg/day) were elevated by about 50% when cimetidine (300mg tid), a known drug metabolising enzyme inhibitor, was co-administered to steady state. Consideration should be given to using doses of APO-PAROXETINE towards the lower end of the range when co-administered with known drug metabolising enzyme inhibitors. Co-administration of a single 30mg dose of paroxetine to subjects receiving chronic daily dosing with 300mg phenytoin, a known metabolising enzyme inducer, is associated with decreased plasma levels of paroxetine (AUC reduced approximately 30%). No initial dosage adjustment of APO-PAROXETINE is considered necessary when the drug is to be administered with known drug metabolising inducers (e.g. carbamazepine, phenytoin, sodium valproate). Any subsequent dosage adjustment should be guided by clinical effect.

Clinical studies have shown that the absorption and pharmacokinetics of paroxetine is unaffected or only marginally affected (i.e. at a level which warrants no change in dosing regimen) by food, antacids, digoxin, and propranolol.

Serotonergic drugs

As with other SSRIs, co-administration with serotonergic drugs (including MAOIs, L-tryptophan, triptans, tramadol, linezolid, SSRIs, lithium and St. John's Wort - *Hypericum perforatum* - preparations) may lead to an incidence of 5-HT associated effects (serotonin syndrome: see Contraindications and Warnings and Precautions).

Caution should be advised and a closer clinical monitoring is required when these drugs are combined with paroxetine.

Pimozide

Increased pimozide levels have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with paroxetine. While the mechanism of this interaction is unknown,



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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 Contraindications).

Overdosage

Overdose of paroxetine (up to 2000mg), alone and in combination with other drugs have been reported. The symptoms of paroxetine overdose include nausea, vomiting, drowsiness, sinus tachycardia, tremor, dilated pupils, dry mouth, irritability, sedation, dizziness, sweating and facial flush. Following the overdose of paroxetine alone, there have been no reports of coma or convulsions. Fatal outcomes have been reported very rarely and generally when paroxetine was taken in combination with other agents.

No specific antidote is known. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Establish and maintain an airway; ensure adequate oxygenation and ventilation. The stomach should be emptied either by the induction of emesis, lavage or both. Following evacuation, 20 –30 grams of activated charcoal may be administered every 4 – 6 hours during the first 24 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of paroxetine, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

Pharmaceutical Precautions

Store below 25°C. Protect from heat light and moisture.

Medicine Classification

Prescription Only Medicine

Package Quantities

Blister packs of 30, 90 and 100 tablets.

Further Information

Contains Lactose.

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