Paxil™ CR

Paroxetine

Controlled Release Tablets

COMPOSITION

Paxil™ CR 12,5 mg: Each controlled release tablet contains: Paroxetine (as Hydrochloride Hemihydrate) 12,5 mg, excipients q.s.

Paxil™ CR 25 mg: Each controlled release tablet contains: Paroxetine (as Hydrochloride Hemihydrate) 25 mg, excipients q.s.

Excipients: Lactose Monohydrate, Hypromellose, Povidone, Silicone Dioxide, Magnesium Stearate.

PHARMACOLOGICAL PROPERTIES

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

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

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 the therapeutic effects of Paroxetine.

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

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.

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.

THERAPEUTIC INDICATIONS

Adults

Major Depressive Disorder:

Paxil™ CR controlled release tablets are indicated for the treatment of major depressive disorder.

Panic Disorder:

Paxil™ CR Controlled release tablets have been shown to be effective in the treatment of panic disorder with or without agoraphobia.

Premenstrual Dysphoric Disorder:

Paxil™ CR controlled release tablets are indicated for the treatment of premenstrual dysphoric disorder (PMDD).

Social Anxiety Disorder/Social Phobia:

Paxil™ CR controlled release tablets have been shown to be effective in the treatment of Social Anxiety Disorder/Social Phobia.

The effectiveness of **Paxil™ CR** controlled release tablets in the long-term treatment of Social Anxiety Disorder/Social Phobia has not been evaluated. Therefore, if **Paxil™ CR** controlled release tablets are to be administered for extended periods in the treatment of Social Anxiety Disorder/Social Phobia, the physician should periodically re-evaluate the long-term usefulness of **Paxil™ CR** for the individual patient.

Children and adolescents (less than 18 years)

All Indications:

Paxil™ CR is not indicated for use in children or adolescents aged less than 18 years (*See Special Warnings and Special Precautions for Use*).

The efficacy of **Paxil™ CR** controlled release tablets has not been studied in children or adolescents aged less than 18 years; however, controlled clinical studies with **Paxil™** tablets in children and adolescents with major depressive disorder failed to demonstrate efficacy, and do not support the use of **Paxil™** in the treatment of depression in this population (*See Special Warnings and Special Precautions for Use*).

The safety and efficacy of **Paxil™** in children aged less than 7 years has not been studied.

CONTRAINDICATIONS

Known hypersensitivity to Paroxetine and excipients.

Paxil™ CR controlled release tablets should not be used in combination with monoamine oxidase (MAO) inhibitors (including linezolid, an antibiotic which is a reversible non selective MAO inhibitor) or within 2 weeks of terminating treatment with MAO inhibitors. Likewise, MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with **Paxil™ CR** controlled release tablets (*See Interaction with other medicinal products and other forms of interaction*).

Paxil™ CR controlled release tablets 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 Interaction with other medicinal products and other forms of interaction*).
Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.

Paxil™ CR controlled release tablets should not be used in combination with pimozide (*See Interaction with other medicinal products and other forms of interaction*).

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Children and Adolescents (less than 18 years)

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. In clinical trials of **Paxil™** in children and adolescents, undesirable effects related to suicidality (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in patients treated with **Paxil™** compared to those treated with placebo (*See 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 **Paxil™ CR**. An analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (prospectively defined as aged 18-24 years) treated with Paroxetine compared with placebo (17/776 [2,19%] versus 5/542 [0,92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and 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 (11/3 455 [0,32%] versus 1/1 978 [0,05%]; all of the events were suicide attempts). However, the majority of these attempts for Paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. 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 **Paxil™** is prescribed can be associated with an increased risk of suicidal behaviour, and these conditions may also 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; 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 **Paxil™** 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 **Paxil™** treatment, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with **Paxil™** should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. **Paxil™** should not be used in combination with serotonin-precursors (such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome (*See Contraindications and Interaction with other medicinal products 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.

Monoamine Oxidase Inhibitors

Treatment with **Paxil™ CR** should be initiated cautiously at least 2 weeks after terminating treatment with MAO inhibitors and dosage of **Paxil™ CR** should be increased gradually until optimal response is reached (*See Contraindications, Interaction with other medicinal products and other forms of interaction*).

Renal/hepatic impairment

Caution is recommended in patients with severe renal impairment or in those with hepatic impairment. *(See Posology and Method of Administration).*

Epilepsy

As with other antidepressants, **Paxil™ CR** should be used with caution in patients with epilepsy.

Seizures

Overall the incidence of seizures is less than 0,1% in patients treated with Paroxetine. The drug should be discontinued in any patient who develops seizures.

ECT

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

Glaucoma

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

Hyponatraemia

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

Haemorrhage

Skin and mucous membrane bleedings (including gastrointestinal bleeding) have been reported following treatment with Paroxetine. Paroxetine should therefore be used with caution in patients concomitantly treated with drugs that give an increased risk for bleeding, and in patients with a known tendency for bleeding or those with predisposing conditions.

Cardiac Conditions

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

Symptoms seen on discontinuation of Paxil™ treatment in adults:

In clinicals trials in adults, undesirable effects seen on treatment discontinuation occurred in 30% of patients treated with **Paxil™** compared to 20% of patients treated with placebo.

The occurrence of discontinuation symptoms is not the same as the drug being addictive or dependence producing as with a substance of abuse.

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

Symptoms seen on discontinuation of Paxil™ treatment in children and adolescents:

In clinical trials in children and adolescents, undesirable effects seen on treatment discontinuation occurred in 32% of patients treated with **Paxil™** compared to 24% of patients treated with placebo. Events reported upon discontinuation of **Paxil™** at a frequency of at least 2% of patients and which occured at a rate at least twice that of placebo were: emotional lability (including suicidal ideation, suicide attempt, mood changes and tearfulness), nervousness, dizziness, nausea and abdominal pain (*See Undesirable Effects*).

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Serotonergic drugs

As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5-HT associated effects (serotonin syndrome: *See Special Warnings and Special Precautions for Use*). Caution should be advised and a closer clinical monitoring is required when serotonergic drugs (such as L-tryptophan, triptans, tramadol, SSRIs, lithium and St. John's Wort – Hypericum perforatum – preparations) are combined with **Paxil™ CR**. Concomitant use of **Paxil™ CR** and MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor) is contraindicated (*See 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 **Paxil™ CR** controlled release tablets is contraindicated (*See 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.

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 Contraindications*), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol.

Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by Paroxetine may lead to reduced plasma concentrations of an active metabolite and hence reduced efficacy of tamoxifen.

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.

Clinical studies have shown the absorption and pharmacokinetics of Paroxetine to be unaffected or only marginally affected (i.e. at a level which warrants no change in dosing regimen) by:

- **food**
- **antacids**
- **digoxin**
- **propranolol**
- **alcohol:** Paroxetine does not increase the impairment of mental and motor skills caused by alcohol, however, the concomitant use of **Paxil™** and alcohol is not advised.

PREGNANCY AND LACTATION

Pregnancy

Animal studies have not shown any teratogenic or selective embryotoxic effects.

Recent epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants in the first trimester have reported an increase in the risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septal defects), associated with the use of Paroxetine. The data suggest that the risk of having an infant with a cardiovascular defect following maternal Paroxetine exposure is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population.

The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant, and should only prescribe **Paxil™ CR** if the potential benefit outweighs the potential risk. If a decision is taken to discontinue **Paxil™ CR** treatment in a pregnant woman, the prescriber should consult *Posology and Method of Administration - Discontinuation of* **Paxil™** and *Special Warnings and Special Precautions for Use – Symptoms seen on discontinuation of* **Paxil™** *treatment in adults.*

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.

Neonates should be observed if maternal use of **Paxil™** continues into the later stages of pregnancy, because there have been reports of complications in neonates exposed to **Paxil™** 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.

In one epidemiological study, the use of SSRIs (including Paroxetine) after the first 20 weeks of pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The absolute risk among those who used SSRIs late in pregnancy was reported to be about 6 to 12 per 1 000 women, compared to 1 to 2 per 1 000 women in the general population.

Lactation

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

Although Paroxetine does not increase the mental and motor skill impairments caused by alcohol, the concomitant use of **Paxil™ CR** and alcohol is not advised.

UNDESIRABLE EFFECTS

Some of the undesirable effects listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Undesirable drug effects are listed below by system organ class and frequency. Frequencies are defined as: very common (1/10), common (1/100, <1/10), uncommon (1/1 000, <1/100), rare (1/10 000, <1/1 000), very rare (<1/10 000), including isolated reports. Common and uncommon events were generally determined from pooled safety data from a clinical trial population of >8 000 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 (mostly ecchymosis).

Very rare: thrombocytopenia.

Immune system disorders

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

Endocrine disorders

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

Metabolism & 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.
Uncommon: confusion, hallucinations.
Rare: manic reactions.

These symptoms may be due to the underlying disease.

Nervous system disorders

Common: dizziness, tremor, headache.
Uncommon: extrapyramidal disorders.
Rare: convulsions, akathisia.
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 Special Warnings and Special Precautions for Use*).
Very rare: acute glaucoma.

Cardiac disorders

Uncommon: sinus tachycardia.

Vascular disorders

Uncommon: postural hypotension.

Respiratory, thoracic and mediastinal disorders

Common: yawning.

Gastrointestinal disorders

Very common: nausea.
Common: constipation, diarrhoea, 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, body weight gain.
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 **Paxil™** (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 Posology and Method of Administration & Special Warnings and Special Precautions for Use*).

Undesirable Effects from Paediatric Clinical Trials

In paediatric clinical trials the following undesirable effects, 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 **Paxil™** 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 Special Warnings and Special Precautions for Use*).

INCOMPATIBILITIES

There are no known incompatibilities with **Paxil™ CR** controlled release tablets.

POSOLOGY AND METHOD OF ADMINISTRATION

Adults

Paxil™ CR controlled release tablets should be administered as a single daily dose, usually in the morning, with or without food. Patients should be informed that **Paxil™ CR** controlled release tablets should not be chewed or crushed, and should be swallowed whole.

Major Depressive Disorder:

The recommended initial dose is 25 mg/day. Some patients not responding to a 25 mg dose may benefit from dose increases in 12,5 mg/day increments, up to a maximum of 62,5 mg/day according to patient response. Dose changes should occur at intervals of at least one week.

As with all antidepressant drugs, dosage should be reviewed and adjusted if necessary within 2 to 3 weeks of initiation of therapy and thereafter as judged clinically appropriate.

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

Panic Disorder:

Patients should begin treatment on 12,5 mg/day and the dose increased weekly in 12,5 mg/day increments according to patient response. Some patients may benefit from having their dose increased up to a maximum of 75 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.

Premenstrual Dysphoric Disorder:

The recommended initial dose is 12,5 mg/day. Some patients not responding to a 12,5 mg dose may benefit from having their dose increased to 25 mg/day. Dose changes should occur at intervals of at least one week.

Patients with PMDD should be periodically assessed to determine the need for continual treatment.

Social Anxiety Disorder/Social Phobia:

The recommended initial dose is 12,5 mg daily. Some patients not responding to a 12,5 mg dose may benefit from having dose increases in 12,5 mg/day increments as required, up to a maximum of 37,5 mg/day according to the patient's response. Dose changes should occur at intervals of at least one week.

General Information:

Elderly:

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

Dosing should commence at 12,5 mg/day and may be increased up to 50 mg/day.

Children and adolescents (less than 18 years):

Paxil™ CR is not indicated for use in children or adolescents aged less than 18 years (*See Therapeutic Indications and Special Warnings and Special Precautions for Use*).

Renal/hepatic impairment:

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

DISCONTINUATION OF Paxil™

As with other psychoactive medications, abrupt discontinuation should generally be avoided (*See Special Warnings and Special Precautions for Use & Undesirable Effects*). The taper phase regimen used in recent clinical trials involved a decrease in the daily dose by 10 mg/day (equivalent to 12,5 mg/day **Paxil™ CR** controlled release tablets) at weekly intervals.

When a daily dose of 20 mg/day (equivalent to 25 mg/day **Paxil™ CR** controlled release tablets) 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.

OVERDOSE

A wide margin of safety is evident from available overdose information on **Paxil™**.

Experience of **Paxil™** in overdose has indicated that, in addition to those symptoms mentioned under Undesirable Effects, vomiting, fever, blood pressure changes, involuntary muscle contractions, anxiety and tachycardia have been reported.

Patients have generally recovered without serious sequelae even when doses of up to 2000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely a fatal outcome, but generally when **Paxil™** was taken in conjunction with other psychotropic drugs with or without alcohol.

No specific antidote is known.

The treatment should consist of those general measures employed in the management of overdose with any antidepressant. Where appropriate, the stomach should be emptied by lavage. Following evacuation, 20 to 30 g of activated charcoal may be administered every 4 to 6 hours during the first 24 hours after ingestion. Supportive care with frequent monitoring of vital signs and careful observation is indicated.

SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30 °C.

PRESENTATIONS

Paxil™ CR 12,5 mg: Box x 30 Controlled release tablets
Paxil™ CR 25 mg: Box x 30 Controlled release tablets

INSTRUCTIONS FOR USE AND HANDLING

No special instructions.

Paxil™ CR is a trademark of the GlaxoSmithKline group of companies

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GlaxoSmithKline

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