Paroxetine hydrochloride hemihydrate

Qualitative and Quantitative Composition

Each PAXIL CR (controlled release) tablet contains paroxetine hydrochloride hemihydrate equivalent to 12.5 mg or 25 mg paroxetine free base.

Pharmaceutical Form

12.5 mg tablets: Yellow, round, biconvex tablets with GSK engraved on one side and 12.5 on the other side.

25 mg tablets: Pink, round, biconvex tablets with GSK engraved on one side and 25 on the other side.

Clinical Particulars

Indications

Adults

Major Depressive Disorder

PAXIL CR tablets are indicated for the treatment of major depressive disorder (MDD).

Panic Disorder

PAXIL CR tablets have been shown to be effective in the treatment of panic disorder with or without agoraphobia.

Premenstrual Dysphoric Disorder

PAXIL CR tablets are indicated for the treatment of premenstrual dysphoric disorder (PMDD).

Social Anxiety Disorder/Social Phobia

PAXIL CR tablets have been shown to be effective in the treatment of Social Anxiety Disorder/Social Phobia.

The effectiveness of PAXIL CR tablets in the long-term treatment of Social Anxiety Disorder/Social Phobia has not been evaluated. Therefore, if PAXIL CR 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 Warnings and Precautions).

The efficacy of PAXIL CR tablets has not been studied in children or adolescents aged less than 18 years; however, controlled clinical studies with PAXIL IR (immediate release) 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 Warnings and Precautions).

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

Dosage and Administration

Adults

PAXIL CR tablets should be administered as a single daily dose, usually in the morning, with or without food. Patients should be informed that PAXIL CR 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 1 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 recognized 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 1 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 1 week.
General Information

Other Populations

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 indications, Warnings and Precautions).

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 Warnings and Precautions, Adverse Reactions). 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 of CR tablets) at weekly intervals. When a daily dose of 20 mg/day (equivalent to 25 mg/day of CR tablets) was reached, patients were continued on this dose for 1 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

Known hypersensitivity to paroxetine and its excipients.

PAXIL CR tablets should not be used in combination with monoamine oxidase inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthionium 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 PAXIL CR tablets (see Interactions).

PAXIL CR 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 Interactions). 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 tablets should not be used in combination with pimozide (see Interactions).

Warnings and Precautions

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, 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 PAXIL compared to those treated with placebo (see Adverse Reactions). Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral 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 to 24 years) treated with paroxetine compared to placebo (17 to 19% versus 6.5% [0.92%]), although this difference was not statistically significant. In 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.

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 ideation and these conditions may also be comorbid 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 recognized 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; Adverse Reactions).

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 characterized 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 (characterized 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-precurors (such as L-tryptophan, oxtiprint) due to the risk of serotonin syndrome (see Contraindications, 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 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 PAXIL CR as a result of paroxetine’s irreversible inhibition of CYP2D6 (see Interactions). This risk may increase with longer duration of co-administration. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

Bone Fracture

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

Monoamine Oxidase Inhibitors

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

Renal/hepatic Impairment

Caution is recommended in patients with severe renal impairment or in those with hepatic impairment (see Dosage and Administration).

Epilepsy

As with other antidepressants, PAXIL CR should be used with caution in patients with epilepsy.
Fertility

Clinical studies have shown that SSRIs (including PAXIL) may affect sperm quality. This effect appears to be reversible following discontinuation of treatment. Changes in sperm quality may affect fertility in some men.
### Blood & Lymphatic System Disorders
- **Uncommon**: abnormal bleeding, predominantly of the skin and mucous membranes.
- **Very rare**: thrombocytopenia.

### Immune System Disorders
- **Very rare**: severe allergic reactions (including anaphylactoid reactions and angioedema).

### Endocrine Disorders
- **Very rare**: syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

### Metabolism & 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.

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.

### Vascular Disorders
- **Uncommon**: postural hypotension.

### Respiratory, Thoracic and Mediastinal Disorders
- **Common**: yawning.

### Gastrointestinal Disorders
- **Very common**: nausea.
- **Common**: constipation, diarrhea, vomiting, dry mouth.
- **Very rare**: gastrointestinal bleeding.

### Hepatobiliary Disorders
- **Rare**: elevation of hepatic enzymes.
- **Very rare**: hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure).

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

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 and alpha2 receptors, 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.

Behavioral 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
Absorption
Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. PAXIL CR tablets control the dissolution rate of paroxetine over a period of four to five hours. In addition to controlling the rate of drug release in vivo, an enteric coat delays the start of drug release until PAXIL CR tablets have left the stomach. Compared to immediate release formulations of paroxetine, controlled release tablets have a reduced absorption rate.

Due to first-pass metabolism, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. Steady state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled release formulations 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).

Metabolism
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.

Elimination
Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in faeces, probably via the bile, of which 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 Patient Populations

Elderly and Renal/Hepatic Impairment
Increased plasma concentrations of paroxetine occur in elderly subjects, in subjects with severe renal and in those with hepatic impairment, but the range of plasma concentrations overlaps that of healthy adult subjects.

Pre-Clinical 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.

Pharmaceutical Particulars

List of Excipients
Tablet cores: Hypromellose; Povidone; Lactose Monohydrate; Magnesium Stearate; Colloidal silicon dioxide; Glycerol behenate; and the following colourants: Yellow Ferric Oxide (12.5 mg tablets) and Red Ferric Oxide (25 mg tablets).
Tablet coating: Methacrylic Acid Copolymer Dispersion; Talc; Triethyl citrate, Opadry Yellow, YS-1-2007 (12.5 mg tablets, includes the coloring agent Sunset Yellow Lake (FD&C Yellow No. 6 aluminium lake)), Opadry Pink, Y-1-1262 (25 mg tablets).

Incompatibilities
There are no known incompatibilities with PAXIL CR tablets.

Shelf-Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Store at a temperature not exceeding 25°C.

Nature and Contents of Container
Foil blister packs or HDPE bottles with child-resistant closures.

Instructions for Use/Handling
No special instructions.

Not all presentations are available in every country.

Version: GDS44/IPI23
Date of issue: 16 August 2017

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