Paxil CR

Version GDS48/IPI26

Paxil CR

Paroxetine hydrochloride hemihydrate

Qualitative and Quantitative Composition

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

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

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

Clinical Features

Directions

Adults

Major depressive disorder

The ***PAXIL CR*** tablet formulation is indicated in the treatment of major depressive disorder (MDD).

Panic Disorder

The ***PAXIL CR*** tablet formulation has been shown to be effective in the treatment of panic disorder, with or without agoraphobia.

Premenstrual Dysphoric Disorder

The ***PAXIL CR*** tablet formulation is indicated in the treatment of premenstrual dysphoric disorder (PMDD).

Social Anxiety Disorder/Social Phobia

The ***PAXIL CR*** tablet formulation has been shown to be effective in the treatment of Social Anxiety Disorder/Social Phobia.

The efficacy of the ***PAXIL CR*** tablet formulation in the long-term treatment of Social Anxiety Disorder/Social Phobia has not been evaluated. Therefore, if the PAXIL CR tablet formulation is to be used in the treatment of Social Anxiety Disorder/Social Phobia for extended periods, the physician should periodically reevaluate the long-term usefulness of the ***PAXIL CR*** formulation in each patient.

Children and Adolescents (Under 18 Years of Age)

All Indications

The use of the ***PAXIL CR*** formulation is not indicated in children or adolescents under 18 years of age (*see WARNINGS and PRECAUTIONS*).

The efficacy of the PAXIL CR tablet formulation has not been studied in children or adolescents below 18 years of age; however, controlled clinical studies, conducted with the PAXIL IR (*immediate-release)* tablet formulation, in children and adolescents with major depressive disorder, have not been able to demonstrate efficacy, so they 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*** have not been studied in children younger than 7 years of age.

Dosage and Administration

Pharmaceutical Presentation

Controlled-release tablets

Adults

The ***PAXIL CR*** tablet formulation should be administered as a single daily dose, usually in the morning, with or without food. Patients should be advised that ***PAXIL CR*** tablets should not be chewed or split, but swallowed whole.

Major depressive disorder

The recommended starting dose is 25 mg/day. Some patients who do not respond to the 25 mg dose may benefit from dose increases, with increments of 12.5 mg/day, up to a maximum of 62.5 mg/day, depending on the patient's response. Dosage changes should be made at intervals of at least one week.

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

Patients suffering from depression should be treated for a sufficient period of time to ensure that they are symptom-free. This period can be several months.

Panic Disorder

Patients should initiate treatment with 12.5 mg/day, increasing the dose weekly in increments of 12.5 mg/day, according to the patient's response. Some patients may benefit from increases in dosage to a maximum of 75 mg/day.

A low starting dose is recommended to minimize the potential aggravation of panic symptoms, which are generally recognized to occur early in the treatment of this disorder.

Patients suffering from panic disorder should be treated for a sufficient period of time to ensure that they are symptom-free. This period can be several months, or even longer.

Premenstrual Dysphoric Disorder

The recommended starting dose is 12.5 mg/day. Some patients who do not respond to the 12.5 mg dose may benefit from increases in dosage to 25 mg/day. Dosage changes should be made at intervals of at least one week.

Patients with PMDD should be evaluated periodically to determine the possible need for continued treatment.

Social Anxiety Disorder/Social Phobia

The recommended starting dose consists of 12.5 mg daily. Some patients who do not respond to the 12.5 mg dose may benefit from dosage increases, with increments of 12.5 mg/day as required, up to a maximum of 37.5 mg/day, depending on patient response. Dosage changes should be made at intervals of at least one week.

Overview

Other towns

Elderly Patients

Increases in plasma concentrations of paroxetine occur in elderly subjects, but the range of concentrations partially coincides with that observed in younger subjects.

Dosing should be started at 12.5 mg/day, and may be increased to 50 mg/day.

Children and Adolescents (Under 18 Years of Age)

The use of the ***PAXIL CR*** formulation is not indicated in children or adolescents under 18 years of age (*see INDICATIONS, WARNINGS AND PRECAUTIONS*).

Renal/hepatic impairment

In patients with severe renal impairment (creatinine clearance <30 m*L*/min), or in those with hepatic impairment, increases in plasma concentrations of paroxetine occur. The dosage should be restricted to the lower limit of the range.

Discontinuation of *PAXIL* Therapy

As with other psychoactive medications, abrupt discontinuation of treatment should generally be avoided (*see WARNINGS AND PRECAUTIONS, ADVERSE EFFECTS*). The tapering regimen, which was used in recent clinical trials, involved a reduction in daily dose of 10 mg/day (equivalent to 12.5 mg/day in CR tablets) at weekly intervals.

When a daily dose of 20 mg/day (equivalent to 25 mg/day in CR tablets) was reached, patients continued this dose for one week before stopping treatment. If intolerable symptoms occur after reducing the dosage, or when stopping treatment, then restoration of the previously prescribed dose may be considered. Subsequently, the doctor may continue to decrease the dosage, but at a more gradual rate.

Contraindications

Known hypersensitivity to paroxetine and excipients.

The ***PAXIL CR*** tablet formulation should not be used in combination with monoamine oxidase (MAO) inhibitors (including linezolid, an antibiotic that is a reversible non-selective MAO inhibitor, and methylthioninium chloride (methylene blue), or within two weeks of termination of treatment with them. Similarly, MAO inhibitor therapy should not be introduced within two weeks of discontinuation of therapy with the ***PAXIL CR*** tablet formulation (see Interactions).

PAXIL CR should not be used in patients receiving medicinal products that can prolong the QT interval and which are also metabolised by CYP450 2D6, such as thioridazine or pimozide (see Interactions).

Warnings and Precautions

Children and Adolescents (Under 18 Years of Age)

Treatment with antidepressant agents is associated with an increased risk of suicidal thoughts and behavior in children and adolescents suffering from Major Depressive Disorder (MDD) and other psychiatric disorders. In clinical trials of PAXIL in children and adolescents, adverse effects related to suicidality (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were observed more frequently in patients treated with ***PAXIL*** than in those treated with placebo (*see ADVERSE EFFECTS*).Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development are lacking.

Clinical Aggravation and Risk of Suicide in Adults

Young adults, especially those with MDD, may be at increased risk of experiencing suicidal behavior during treatment with ***PAXIL CR.*** An analysis of placebo-controlled studies in adults with psychiatric disorders demonstrated a higher frequency of incidence of suicidal behavior in young adults (prospectively defined in the age range 18-24 years) treated with paroxetine compared to those treated with placebo.(17/776 [2.19%] vs. 5/542 [0.92%]), although this difference was not statistically significant. No such increase was observed in the older patient groups (25 ~~***to 64***~~ years of age and ≥65 years of age). In adults with MDD (of all ages), a statistically significant increase in the incidence of suicidal behavior was observed in patients treated with paroxetine compared to those treated with placebo (11/3455 [0.32%] vs. 1/1978 [0.05%]; all events were suicide attempts). However, in the group of patients treated with paroxetine, the majority of these attempts (8 out of 11) took place in younger adults, aged 18 ~~***to 30***~~ years. These data on MDD suggest that the increased incidence frequency observed in the population of young adults with psychiatric disorders may extend beyond the age of 24 years.

Depressed patients may experience worsening of their depressive symptoms and/or suicidal ideation and behavior (suicidality), regardless of whether or not they are being treated with antidepressant medications. The risk persists until significant remission occurs. Existing general clinical experience with all antidepressant therapies indicates a possible increased risk of suicide in patients who are in the early stages of recovery. It is possible that other psychiatric disorders, for which ***PAXIL*** is prescribed, are associated with an increased risk of suicidal behavior and, in addition, these disorders could also be comorbidities associated with some MDD. In addition, patients with a history of suicidal thoughts or behaviors, young adults, and those patients who exhibit some significant degree of suicidal ideation prior to starting treatment, are at an increased risk of experiencing suicidal thoughts or attempts. All patients should be monitored for clinical aggravation (including development of new symptoms) and suicidality throughout treatment, especially at the beginning of a treatment course or at the time of dosage changes, either increases or decreases.

Patients (and caregivers) should be advised that surveillance is necessary to determine any worsening of their disease (including the development of new symptoms) and/or the emergence of suicidal ideation/behavior or thoughts of self-harm, and to seek medical advice immediately if these symptoms occur. The fact that the initiation of some symptoms, such as agitation, akathisia or mania, may be related to the underlying disease state or to drug therapy should be recognized (*see below Akathisia and Manic and Bipolar Disorder; Adverse Effects*).

Modification of the therapeutic regimen, including possible discontinuation of the medicinal product, should be considered in patients who experience clinical aggravation (including the development of new symptoms) and/or the emergence of suicidal ideation/behavior, especially if these symptoms are severe, abrupt onset, or were not part of the patient's symptoms.

Akathisia

Rarely, the use of ***PAXIL***, or other selective serotonin reuptake inhibitors (SSRIs), has been associated with the development of akathisia, which is characterized by an internal situation of restlessness and psychomotor agitation, such as inability to sit or sit still, which usually It is associated with subjective discomfort. This condition is very likely to occur within the first few weeks of treatment.

Serotonin Syndrome/Neuroleptic Malignant Syndrome

Rarely, there is a possibility of development of serotonin syndrome-like events, or neuroleptic malignant syndrome, associated with ***PAXIL*** treatment, particularly when administered in combination with other serotonergic or neuroleptic drugs, or both. As these syndromes can lead to life-threatening disorders, should these events occur (characterized by clusters of symptoms, such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations in vital signs, changes in mental status including confusion, irritability, extreme agitation progressing to delirium, and coma), treatment with ***PAXIL*** should be discontinued. and initiating supportive symptomatic treatment. The ***PAXIL*** formulation should not be used in combination with serotonin precursors (such as L-tryptophan, oxytriptan), due to the risk of occurrence of serotonin syndrome (*see Contraindications* ~~*e,*~~ *Interactions).*

Manic and Bipolar Disorder

There is a possibility that a major depressive episode is the initial presentation of bipolar disorder. It is generally agreed (although not established in controlled trials) that treating such an episode with an antidepressant agent alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Before initiating treatment with any antidepressant, patients should be properly screened to determine if they are at risk for bipolar disorder; These screening tests should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that paroxetine has not been approved for use in the treatment of bipolar depression. As with all antidepressant agents, paroxetine should be used with caution in patients with a history of mania.

Tamoxifen

Some studies have shown that the efficacy profile of tamoxifen, quantified through the risk of breast cancer recurrence/mortality, may be reduced when prescribed concomitantly with PAXIL CR, as a result of paroxetine's irreversible inhibition of the CYP2D6 isoenzyme (see Interactions). This risk could increase proportionally with the duration of co-administration. When tamoxifen is used in the treatment or prevention of breast cancer, prescribing physicians should consider the use of an alternative antidepressant with little or no inhibitory effect on the CYP2D6 isoenzyme.

Broken Bones

Epidemiological studies conducted to assess the risk of experiencing bone fractures after exposure of patients to some antidepressants, including SSRIs, have reported that there is an association with fractures. The risk occurs during treatment and peaks in the early stages of therapy. In the care of patients treated with ***PAXIL***, the possibility of fractures should be considered.

Monoamine oxidase inhibitors

Treatment with PAXIL CR should be initiated cautiously at least two weeks after completion of MAO inhibitor therapy; the dose of ***PAXIL CR*** should be gradually increased until an optimal response is achieved (*see CONTRAINDICATIONS, INTERACTIONS*).

Renal/hepatic impairment

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

Epilepsy

As with other antidepressant agents, the ***PAXIL CR*** formulation should be used with caution in patients with epilepsy.

Seizures

The overall incidence of seizures is less than 0.1% in patients treated with paroxetine. Drug administration should be discontinued in any patient who develops seizures.

Electroconvulsive Therapy (ECT)

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

Glaucoma

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

Hyponatremia

Hyponatriaemia has been reported rarely, predominantly in the elderly. Hyponatremia usually reverses when paroxetine is discontinued.

Haemorrhage

Cases of bleeding into the skin and mucous membranes (including gastrointestinal and gynaecological bleeding) have been reported following treatment with paroxetine. Therefore, paroxetine should be used with caution in patients receiving concomitant treatment with drugs that represent an increased risk of bleeding, as well as in patients with a known tendency to bleed, or who have predisposing disorders(see ADVERSE REACTIONS). SSRIs May Increase Risk of Postpartum Hemorrhage

Heart Disorders

The usual precautions should be taken in patients suffering from cardiac disorders.

QT prolongation

Cases of QT prolongation have been reported, although causality has not been established with PAXIL CR.

PAXIL CR should be used with caution in patients with a history of QT prolongation, patients taking antiarrhythmic medications or other medications that can potentially prolong the QT interval, or those with relevant pre-existing heart disease.

For more information see Contraindications and Interactions.

Symptoms Seen When Discontinuing *PAXIL* Treatment in Adults

In clinical trials in adults, adverse effects observed upon discontinuation of treatment occurred in 30% of patients treated with ***PAXIL*** compared with 20% of those treated with placebo. The occurrence of post-discontinuation symptoms is not the same as when the drug becomes addictive or produces dependence, as in the case of substances that produce substance abuse.

Dizziness, sensory disturbances (including paresthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremors, confusion, sweating, headache, diarrhoea have been reported. Usually these symptoms are mild to moderate, although in some patients they can be severe. They usually occur within the first few days after stopping treatment, but very rare reports of these symptoms have occurred in patients who have inadvertently missed a dose. These symptoms usually resolve spontaneously within two weeks, although in some individuals they may be longer (~~***two***~~ to three months or more). Therefore, it is advisable to gradually reduce the dosage of ***PAXIL*** when treatment is discontinued for a period of several weeks or months, according to the patient's needs (*see "Discontinuation of* ***PAXIL*** Therapy*", Dosage and Administration*).

Sexual dysfunction

SSRIs can cause sexual dysfunction (see Adverse Effects). There have been reports of prolonged sexual dysfunction wheresymptoms have continued despite stopping SSRIs.

Symptoms Seen When Discontinuing *PAXIL* Treatment in Children and Adolescents

In clinical trials in children and adolescents, adverse effects observed upon discontinuation of treatment occurred in 32% of patients treated with ***PAXIL***, compared with 24% of patients treated with placebo. Events reported upon discontinuation of ***PAXIL***, which had a frequency of occurrence of at least 2% of patients and occurred at a rate at least twice that of placebo, were: emotional instability (including suicidal ideation, suicide attempt, mood changes and crying), nervousness, dizziness, nausea and abdominal pain (*see Adverse Effects*).

PAXIL CR, only in 12.5 mg tablets

The coating of the 12.5 mg paroxetine controlled-release tablet (Opadry Yellow: YS-1-2007) contains the twilight yellow coloring agent (FD&C Yellow No. 6 aluminum lake), an azo dye that can cause allergic reactions.

Interactions

Serotonergic Drugs

As with other SSRIs, concurrent administration with serotonergic drugs may lead to an incidence of effects associated with 5HT (serotonin syndrome; see WARNINGS and PRECAUTIONS). Caution and close medical supervision are advised when using serotonergic drugs (such as L-tryptophan, triptans, tramadol, SSRIs, lithium, fentanyl and St. John's wort preparations - Hypericum perforatum) in combination with ***PAXIL CR.***

Concomitant use of ***PAXIL*** CR and MAO inhibitors (including linezolid, an antibiotic that is a reversible nonselective MAO inhibitor, and methylthioninium chloride (methylene blue)) is contraindicated (see CONTRAINDICATIONS).

Pimozide

In a study with a low, single dose of pimozide (2 mg), an increase in pimozide concentrations was demonstrated when coadministered with paroxetine. This is explained by the known inhibitory properties of paroxetine on CYP2D6. Concomitant use of pimozide and ***PAXIL CR*** tablets is contraindicated due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval (*see CONTRAINDICATIONS*).

Drug Metabolizing Enzymes

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

When paroxetine is administered concurrently with a known inhibitor ofdrug metabolising drugs, doses at the lower limit of the range should be considered.

No initial dosage adjustment is considered necessary when administering the drug concurrently with knowninducers of drug metabolising drugs (e.g., carbamazepine, rifampicin, phenobarbital, phenytoin). Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

Fosamprenavir/Ritonavir: Concurrent administration of fosamprenavir/ritonavir with paroxetine significantly decreases plasma concentrations of paroxetine. Any dosage adjustment should be made by monitoring the clinical effect (tolerability and efficacy).

Procyclidine

Daily administration of paroxetine significantly increases plasma concentrations of procyclidine. If anticholinergic effects are observed, a reduction in the dosage of procyclidine should be made.

Anticonvulsants

carbamazepine, phenytoin, sodium valproate. Concomitant administration does not appear to show any effect on the pharmacokinetic/pharmacodynamic profile in epileptic patients.

Neuromuscular Blockers

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

CYP2D6 inhibitory potency of paroxetine

As with other antidepressant agents, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to an increase in plasma concentrations of concurrently administered drugs, which are metabolized by this enzyme. These include certain tricyclic antidepressants (e.g., amitriptyline, nortriptyline, imipramine, and desipramine), phenothiazine-derived neuroleptics (e.g., perphenazine and thioridazine, *see Contraindications*), risperidone, atomoxetine, certain type 1c antiarrhythmics (e.g., propafenone and flecainide), and metoprolol.

Tamoxifen has an important active metabolite, endoxifen, which is produced by the CYP2D6 isoenzyme and contributes significantly to the efficacy profile of tamoxifen. Irreversible inhibition of the CYP2D6 isoenzyme by paroxetine leads to a reduction in endoxifen plasma concentrations (see WARNINGS and PRECAUTIONS).

CYP3A4

An *in vivo* interaction study, involving coadministration of paroxetine and terfenadine, a cytochrome CYP3A4 substrate, under steady-state conditions, revealed no effect of paroxetine on the pharmacokinetics of terfenadine. A similar *in vivo* interaction study revealed no effect of paroxetine on the pharmacokinetics of alprazolam, or vice versa. Concurrent administration of paroxetine with terfenadine, alprazolam and other drugs that are substrates of CYP3A4 would not be expected to cause any risk.

Clinical studies have shown that the absorption and pharmacokinetics of paroxetine are not affected, or are only marginally affected (i.e., at a level that does not warrant any change in dosing regimen) by:

- foods
- Antacids
- digoxin
- Propranolol
- alcohol: paroxetine does not increase the impairment of mental and psychomotor skills caused by alcohol; however, concomitant use of ***PAXIL*** and alcohol is not advisable.

Pregnancy and Lactation

Fertility

Some clinical studies show that SSRIs (including ***PAXIL***) affect sperm quality. This effect appears to be reversible after discontinuation of treatment. Changes in sperm quality affect fertility in some men.

Pregnancy

Animal studies have not shown selective teratogenic or embryotoxic effects.

Epidemiological studies on the clinical outcome of pregnancies in which maternal exposure to antidepressants in the first trimester of pregnancy has been followed have reported an increased risk of particularly cardiovascular congenital malformations (e.g., ventricular and atrial septal defects) associated with paroxetine use. The data suggest that the risk of having an infant with a cardiovascular defect after maternal exposure to paroxetine is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population.

The treating physician will need to consider the alternative treatment option in women who are pregnant or planning to become pregnant, and should prescribe ***PAXIL CR*** only if the potential benefit outweighs the potential risk. If a decision is made to discontinue treatment with PAXIL CR in a pregnant woman, the treating physician should refer to the section Dosage and *Administration – Discontinuation of* PAXIL and *Warnings and Precautions – Symptoms observed when discontinuing treatment with* ***PAXIL*** *in adults*.

There have been reports of preterm birth in pregnant women exposed to paroxetine or other SSRIs, although no causal relationship with drug therapy has been established.

Observational data have provided evidence of an increased (less than double) risk of postpartum hemorrhage after exposure to SSRIs one month before birth.

Newborn surveillance should be instituted if maternal use of ***PAXIL*** continues into late pregnancy, as reports of complications have occurred in newborns exposed to ***PAXIL***, or other SSRIs, late in the third trimester of pregnancy. However, no causal association with drug therapy has been confirmed. Reported clinical findings have included: dyspnea, cyanosis, apnea, convulsions, temperature instability, difficulty feeding, vomiting, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremors, nervousness, irritability, lethargy, constant crying, and somnolence. In some cases, reported symptoms were described as neonatal withdrawal symptoms. In most cases, complications were reported to arise immediately after or shortly after delivery (<24 hours).

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

Nursing

Reduced amounts of paroxetine are excreted in breast milk. In published studies, serum concentrations in breastfed infants were either undetectable (<2 nanograms/m L) or very low (<4 nanograms/m*L*). No signs of medicinal effects were observed in these infants. However, the ***PAXIL*** formulation should not be used during breastfeeding unless the expected benefits to the mother justify the potential risks to the infant.

Effects on the Ability to Drive and Operate Machinery

Existing clinical experience has shown that ***PAXIL*** therapy is not associated with any impairment of cognitive or psychomotor functions. However, as with all psychoactive drugs, patients should be warned about their ability to drive cars and operate machinery.

Although paroxetine does not increase the impairment of mental and psychomotor skills caused by alcohol, concomitant use of ***PAXIL CR*** and alcohol is not advisable.

Adverse Effects

Some of the adverse effects listed below may decrease in intensity and frequency of occurrence upon continuation of treatment, so they generally do not lead to discontinuation of therapy.

Drug adverse effects are listed below by organ system class and frequency of occurrence. The frequency of occurrence is defined as: very common (1/10), common (1/100, <1/10), uncommon (1≥≥≥/1 000, <1/100), rare (1/10000, <1/1000), very rare (<1/10000), including isolated communications. Common and uncommon effects were generally determined from global safety data, gathered from a clinical trial population of more than 8000 paroxetine-treated patients, and cited as having a higher incidence of occurrence than the placebo-treated group. Rare and very rare effects were generally determined from post-marketing data and, furthermore, refer to a reported rate rather than a true frequency.≥

Blood and Lymphatic System Disorders

Uncommon: abnormal bleeding, predominantly from the skin and mucous membranes.
Very rare: thrombocytopenia.

Immune System Disorders

Very raresevere allergic reactions (including anaphylactoid reactions and angioedema).

Endocrine Disorders

Very raresyndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolic and Nutritional Disorders

Commonincreases in cholesterol concentrations, decreased appetite.
Raroshiponatremia.

Reported cases of hyponatremia have occurred predominantly in elderly patients and are sometimes due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Psychiatric Disorders

Common, drowsiness, insomnia, agitation, disturbed sleep content (including nightmares).
Uncommonconfusion, hallucinations.
Rare manic reactions.

There is a possibility that these symptoms are due to the underlying disease.

Nervous System Disorders

Common, dizziness, tremors, headache.
Uncommonextrapyramidal disorders.
Rare seizures, akathisia, restless legs syndrome (RLS).
Very rareserotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, tachycardia with chills and tremors).

There have been reports of extrapyramidal disorders, including orofacial dystonia, in patients who sometimes have underlying psychomotor disorders, or who were on neuroleptic therapy.

Eye Disorders

Common blurred vision.
Uncommonmydriasis (see Warnings and Precautions).
Very rareacute glaucoma

Heart Disorders

Uncommonsinus tachycardia.

Vascular Disorders

Uncommonorthostatic hypotension.

Respiratory, Thoracic and Mediastinal Disorders

Common yawns.

Gastrointestinal Disorders

Very commonnausea.
Commonconstipation, diarrhea, vomiting, dry mouth.
Very raregastrointestinal bleeding.

Hepatobiliary disorders

Rarelyelevated liver enzyme levels.
Very rare liver events (such as hepatitis, sometimes associated with jaundice and/or liver failure).

There have been reports of elevations in liver enzyme concentrations. Very rarely, postmarketing reports of liver events (such as hepatitis, sometimes associated with jaundice or hepatic impairment, or both) have also been received. Consideration should be given to stopping paroxetine if there is any prolonged elevation in liver function test results.

Skin and Subcutaneous Tissue Disorders

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

Kidney and Urinary Disorders

Uncommon urinary retention, urinary incontinence.

Breast and Reproductive System Disorders

Very commonsexual dysfunction.
Rarehyperprolactinemia/galactorrhea., menstrual disorders (including menorrhagia, metrorrhagia, and amenorrhea).

General and Administration Site Disorders

Commonasthenia, increased body weight.
Very rare peripheral edema.

Symptoms Seen When Discontinuing Paroxetine Treatment

Common: dizziness, sensory disorders, sleep disorders, anxiety, headache.
Uncommon: agitation, nausea, tremors, confusion, sweating, diarrhea.

As with many psychoactive medications, discontinuation of ***PAXIL*** therapy (particularly when abrupt) may result in symptoms such as dizziness, sensory disturbances (including paresthesia, electric shock sensations, and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, headache, tremors, confusion, diarrhea, and sweating. In most patients these events are mild to moderate and resolve spontaneously. No particular group of patients appears to be at increased risk for these symptoms; therefore, it is advisable that when paroxetine treatment is no longer required, the dose should be gradually discontinued and tapering (*see DOSAGE AND ADMINISTRATION* AND *WARNINGS AND PRECAUTIONS).*

Adverse Effects of Pediatric Clinical Trials

The following side effects were reported in paediatric clinical trials, with a frequency of occurrence of at least 2% of patients and at a rate at least twice that of placebo: emotional instability (including self-harm, suicidal thoughts, suicide attempt, crying and mood fluctuations), hostility, decreased appetite, tremors, sweating, hyperkinesia and agitation. Suicidal thoughts and suicide attempts were mainly observed in clinical trials conducted in adolescents with major depressive disorder. Cases of hostility occurred particularly in children with obsessive-compulsive disorder and, especially, in children under 12 years of age.

In studies using a tapering regimen (reduction of the daily dose by 10 mg/day, at weekly intervals, to a dose of 10 mg/day administered for one week), symptoms reported during the tapering phase, or upon discontinuation of ***PAXIL*** therapy, with a frequency of occurrence of at least 2% of patients and at a rate at least twice that of placebo, were: emotional instability, nervousness, dizziness, nausea and abdominal pain (*see WARNINGS and PRECAUTIONS*).

Overdose

Symptoms and Signs

From the available information regarding overdosage with ***PAXIL***, a wide margin of safety is evident.

Experience with ***PAXIL*** in terms of overdosage has indicated that, in addition to the symptoms mentioned as Adverse Effects, there have been reports of fever, changes in blood pressure, involuntary muscle contractions, anxiety and tachycardia.

Patients have generally recovered without experiencing serious sequelae, even in cases where doses up to 2000 mg were taken alone. Occasionally, events such as coma or ECG changes and, very rarely, fatal outcomes have been reported, but usually when ***PAXIL*** was taken concomitantly with other psychotropic drugs, with or without alcohol.

Treatment

No specific antidote is known.

Treatment should consist of those general measures that are employed to treat an overdose with any antidepressant agent. Supportive care is indicated, with frequent monitoring of vital signs and careful observation. Treatment of patients should be as clinically directed, or as recommended by the national poison control center, where available.

Pharmacological properties

Pharmacodynamics

ATC Code

Anatomical Therapeutic Chemical Code (ATC): N06A B05.

Pharmacotherapeutic group: Antidepressants: selective serotonin reuptake inhibitors.

Mechanism of Action

Paroxetine is a potent and selective inhibitor of serotonin reuptake (5-hydroxytryptamine, 5-HT), in addition, its antidepressant action and its efficacy in the treatment of obsessive-compulsive disorder (OCD) and panic disorder are thought to be related to its specific inhibition of serotonin reuptake in brain neurons.

Paroxetine is not chemically related to tricyclic antidepressants, tetracyclic antidepressants, or other available antidepressants.

Paroxetine has a low affinity for muscarinic cholinergic receptors, as animal studies have indicated that it has only mild anticholinergic properties.

In keeping with this selective action, *in vitro* studies have indicated that, in contrast to tricyclic antidepressants, paroxetine exhibits low affinity for alpha1, alpha2 and beta adrenergic receptors, dopamine (D2), similar to 5-HT1, 5-HT2 and histamine (H1) receptors. This lack of interaction with postsynaptic receptors in *vitro* is substantiated by *in vivo* studies demonstrating the lack of hypotensive and depressive properties of the CNS.

Pharmacodynamic effects

Paroxetine does not affect psychomotor function or potentiate the depressive effects of ethanol.

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

Behavioral and EEG studies indicate that paroxetine is weakly activated, when administered at doses generally higher than 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.

After administration to healthy subjects, paroxetine does not produce clinically significant changes in blood pressure, heart rate and ECG.

Studies indicate that, in contrast to antidepressant agents that inhibit noradrenaline uptake, paroxetine is very unlikely to inhibit the antihypertensive effects of guanethidine.

Pharmacokinetics

Absorption

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

Due to first-pass metabolism, the amount of paroxetine available in the systemic circulation is less than that absorbed from the gastrointestinal tract.

Steady-state systemic concentrations are reached 7 to 14 days after initiation of treatment, either with immediate or controlled release formulations; Pharmacokinetics do not appear to change during long-term therapy.

Distribution

Paroxetine is widely distributed in tissues, as pharmacokinetic calculations indicate that only 1% of paroxetine in the body is found in plasma.

Approximately 95% of paroxetine in plasma is bound to plasma proteins at therapeutic concentrations.

No correlation was found between plasma concentrations of paroxetine and clinical effect (adverse effects and efficacy).

Metabolism

The major metabolites of paroxetine are polar and conjugated products of oxidation and methylation, which are rapidly eliminated. In view of their relative lack of pharmacological activity, they do not appear to contribute to the therapeutic effects of paroxetine.

Metabolism does not compromise the selective action on neuronal 5-HT selective reuptake of paroxetine.

Elimination

Urinary excretion of unchanged paroxetine is generally less than 2% of the dose, while that of metabolites is approximately 64% of the dose. About 36% of the dose is excreted in the faeces, probably through bile, of which unchanged paroxetine accounts for less than 1% of the dose. Therefore, paroxetine is almost completely eliminated by the metabolic pathway.

Excretion of the metabolite is biphasic; Initially, it is a result of first-pass metabolism and is subsequently controlled by systemic elimination of paroxetine.

The elimination half-life is variable, but is usually about one day.

Special Patient Populations

Elderly and Renal/Hepatic Insufficiencies

Increases in plasma concentrations of paroxetine occur in elderly subjects, individuals with severe renal impairment, and those with hepatic impairment, but the range of plasma concentrations partially coincides with that observed in healthy adult subjects.

Preclinical Information

Toxicology studies have been conducted in rhesus monkeys and albino rats; In both, the metabolic pathway is similar to that described in humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. No cases of phospholipidosis were observed in primate studies of up to one year duration at doses six times the recommended clinical dosage limits.

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

Genotoxicity: In a series of *in vitro* and *in vivo* tests, no genotoxicity was observed.

Pharmaceutical Information

List of Excipients

Tablet Cores

Hypromellose; Povidone; Lactose Monohydrate; Magnesium Stearate; Colloidal Silicon Dioxide; Glyceryl Behenate and the following dyes: Yellow Iron Oxide (12.5 mg tablets) and Red Iron Oxide (25 mg tablets).

Tablet Coating

Dispersion of Methacrylic Acid Copolymer; Talc; Triethyl Citrate, Opadry Yellow, YS-1-2007 (12.5 mg tablets, includes twilight yellow coloring agent (FD&C Yellow No. 6 yellow lacquer)), Opadry Rose, Y-1-1262 (25 mg tablets). For important information on some of these excipients, see Warnings and Precautions.

Shelf Life

The expiration date is indicated on the packaging.

Storage

Storage conditions are detailed on the packaging.

Container

Aluminum honeycomb packaging or high-density polyethylene (HDPE) bottles with childproof closure.

Incompatibilities

There are no known incompatibilities with ***PAXIL CR*** tablets.

Use and Management

There are no special instructions.

Not all presentations are available in all countries.

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