
Paxil

Version GDSv48/IPIv33

Paxil

Paroxetine hydrochloride hemihydrate

Qualitative and Quantitative Composition

PAXIL 20 mg Tablets: White, film-coated, oval-shaped, biconvex tablets with a break line on one side.

PAXIL 30 mg Tablets: Blue, film-coated, oval-shaped, biconvex tablets with a break line on one side.

Each **PAXIL** tablet contains paroxetine hydrochloride hemihydrate equivalent to 20 mg or 30 mg paroxetine-free base.

PAXIL Liquid: Orange suspension with orange smell and sweet taste.

PAXIL liquid contains paroxetine hydrochloride hemihydrate equivalent to 20 mg paroxetine-free base per 10 mL (2mg/mL).

Clinical Information

Directions

Adults

Major depressive disorder

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

Results from studies in which patients were treated with **PAXIL** for up to one year indicate that **PAXIL** is effective in preventing relapse and also recurrence of depressive symptoms.

Anxiety Disorders

Treatment of symptoms and prevention of recurrence of Obsessive Compulsive Disorder (OCD).

Treatment of symptoms and prevention of recurrence of Panic Disorder with or without agoraphobia.

Treatment of Social Anxiety Disorder/Social Phobia.

Treatment of symptoms and prevention of recurrence of Generalized Anxiety Disorder.

Treatment of Post-Traumatic Stress Disorder.

Children and Adolescents (Under 18 Years of Age)

All Indications

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

Controlled clinical studies in children and adolescents with major depressive disorder have not demonstrated 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** have not been studied in children younger than 7 years of age.

Dosage and Administration

Dosage form: Film-coated tablets and suspension

Adults

For oral administration.

It is recommended that **PAXIL** be administered once a day, in the morning, with food.

Tablets: The tablets should be swallowed, rather than chewed. The 20 mg and 30 mg tablets have slots that allow the tablets to be split in half for doses of 10 mg and 15 mg doses, respectively, if required.

As with all antidepressant drugs, the dose should be reviewed and adjusted if necessary two to three weeks after initiation of treatment and thereafter as clinically appropriate. Patients should be treated for a sufficient period to ensure that they are symptom-free. This period can be several months for depression and may even be longer for OCD and panic disorder. As with many psychoactive medications, abrupt discontinuation should be avoided (see **ADVERSE REACTIONS**).

Major Depressive Disorder:

The recommended dose is 20 mg per day. In some patients it may be necessary to increase the dose. This should be done gradually, in increments of 10 mg, up to a maximum of 50 mg, according to the patient's response.

Obsessive-Compulsive Disorder

The recommended dose is 40 mg per day. Treatment should be initiated at 20 mg daily and the dose may be increased weekly in 10 mg increments. Some patients will benefit from increasing the dose to a maximum of 60 mg per day.

Panic Disorder

The recommended dose is 40 mg per day. Treatment of patients should be initiated with 10 mg daily and the dose should be increased weekly, in 10 mg increments, according to patient response. Some patients may benefit from increasing their dose to a maximum of 60 mg per day. As is generally recognized, there is potential for worsening of panic symptomatology during initial treatment of panic disorder; therefore, a low starting dose is recommended.

Social Anxiety Disorder/Social Phobia

The recommended dose is 20 mg per day. Patients who do not respond to a dose of 20 mg may benefit from increasing the dose, in 10 mg increments as needed, up to a maximum of 50 mg/day. Dose changes should take place at intervals of at least 1 week according to the patient's response.

Generalized Anxiety Disorder

The recommended dose is 20 mg per day. Some patients who do not respond to a 20 mg dose may benefit from dose increase, in 10 mg increments as needed, up to a maximum of 50 mg/day, depending on the patient's response.

Post-Traumatic Stress Disorder

The recommended dose is 20 mg per day. Some patients who do not respond to a 20 mg dose may benefit from dose increase, in 10 mg increments as needed, up to a maximum of 50 mg/day based on patient response.

Overview

Discontinuation of PAXIL

As with other psychoactive medications, abrupt discontinuation should generally be avoided (see **WARNINGS AND PRECAUTIONS AND ADVERSE REACTIONS**). The phase-out regimen used in recent clinical studies included a daily dose decrease of 10 mg/day at weekly intervals.

When a daily dose of 20 mg/day was reached, patients continued to be treated with this dose for one week before treatment was discontinued. If intolerable symptoms occur after a dose decrease or when treatment is discontinued, then reinstatement of the previously prescribed dose may be considered. Subsequently, the doctor may continue to reduce the dose, but in a more gradual manner.

Other Towns

Elderly

Elderly subjects have higher plasma concentrations of paroxetine, but the range of concentrations overlaps those observed in younger subjects.

Treatment should begin with the initial adult dose and may be increased weekly in 10 mg increments to a maximum of 40 mg daily, depending on the patient's response.

Children and Adolescents (Under 18 Years of Age)

PAXIL is not indicated for use in children or adolescents under 18 years of age (see **DIRECTIONS, WARNINGS, AND PRECAUTIONS**).

Patients with renal/hepatic impairment

Higher plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance of < 30 mL/min) or those with hepatic impairment. The recommended dose is 20 mg per day. Dose increments, if required, should be restricted to the lower end of the range.

Contraindications

Known hypersensitivity to paroxetine and its excipients.

PAXIL must not be used in combination with monoamine oxidase (MAO) inhibitors (including linezolid, an antibiotic that is a reversible non-selective MAO inhibitor, and methylthionium chloride (methylene blue) or within two weeks after stopping treatment with MAO inhibitors. Similarly, treatment with MAO inhibitors should not be initiated within two weeks after cessation of **PAXIL** therapy (see **Interactions**).

PAXIL should not be used in patients receiving medicinal products that may 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 antidepressants is associated with an increased risk of experiencing suicidal thoughts and behaviors in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. In clinical studies of **PAXIL** in children and adolescents, more adverse events related to suicidal behaviour (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were observed in patients treated with **PAXIL** compared to those treated with placebo (see **ADVERSE REACTIONS**). There are no long-term safety data in children and adolescents about growth, maturation, and cognitive and behavioral development.

Clinical Worsening 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**. 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 the possibility that this increased incidence frequency, observed in the population of young adults with psychiatric disorders, extends beyond the age of 24 years.

Patients with depression may experience worsening of their depressive symptoms and/or emergence of suicidal ideation and behaviors (suicidal behavior) whether or not they are taking antidepressant medications. This risk persists until there is significant remission. It is general clinical experience with all antidepressant therapies that the risk of suicide might increase in the initial stages of recovery. Other psychiatric conditions for which **PAXIL** is prescribed may be associated with an increased risk of suicidal behavior and, in addition, these conditions may also be comorbid with MDD. In addition, patients with a history of suicidal thoughts or behaviors, young adults, and patients who exhibit a significant degree of suicidal ideation prior to starting treatment are at increased risk for suicidal thoughts or suicide attempts. All patients should be monitored for clinical aggravation (including development of new symptoms) and suicidal behavior throughout treatment, especially at the beginning of a treatment course or at the time of dosage changes, whether increases or decreases.

Patients (and their caregivers) should be alerted to the need to monitor for any worsening of their condition (including the development of new symptoms) and/or the emergence of suicidal ideation/behavior or thoughts of self-harm, and seek immediate medical advice if these symptoms occur. It should be recognized that the initiation of some symptoms, such as agitation, akathisia, or mania, may be related to the underlying disease state or drug therapy (see below **Akathisia and Mania and Bipolar Disorder; Adverse Reactions**).

A change in the therapeutic regimen, including possible discontinuation of medication, should be considered in patients who experience clinical worsening (including the development of new symptoms) and/or the emergence of suicidal ideation/behavior, especially if these symptoms are severe, abrupt in initiation, 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 feeling of restlessness and psychomotor agitation, such as the inability to sit or stand, and is usually associated with subjective distress. It is more likely to occur in the first few weeks of treatment.

Serotonin Syndrome/Neuroleptic Malignant Syndrome

Rarely, in association with **PAXIL** treatment, the development of serotonin syndrome or neuroleptic malignant syndrome-type events may occur, particularly when this treatment is administered in combination with other serotonergic and/or neuroleptic drugs. As these syndromes can result in life-threatening conditions, treatment with **PAXIL** should be discontinued if such events occur (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations in vital signs, alterations in mental status such as confusion, irritability, extreme agitation progressing to delirium, and coma) and treatment instituted. symptomatic supportive. **PAXIL** should not be used in combination with serotonin precursors (such as tryptophan, oxytryptan) 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 (although not established in clinical studies) that treatment of such an episode with an antidepressant as monotherapy may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Before initiating treatment with an antidepressant, patients should be appropriately selected to determine if they are at risk for bipolar disorder; That selection should include a detailed psychiatric history, including family history of suicide, bipolar disorder, and depression. It should be noted that **PAXIL** is not approved for use in the treatment of 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 profile of tamoxifen, quantified through the risk of breast cancer recurrence/mortality, may be reduced when prescribed concomitantly with **PAXIL**, as a result of paroxetine's irreversible inhibition of the CYP2D6 isoenzyme (see *Interactions*). This risk could increase proportionately with a longer 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 experiencing fractures should be considered.

Monoamine oxidase inhibitors

Treatment with **PAXIL** should be initiated cautiously at least 2 weeks after termination of MAO inhibitor therapy and the dose of **PAXIL** should be gradually increased until optimal response is obtained (see *CONTRAINDICATIONS, INTERACTIONS*).

Patients with Renal/Hepatic Impairment

Caution is advised in patients with severe renal impairment or in those with hepatic impairment (see *DOSAGE AND ADMINISTRATION*).

Epilepsy

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

Seizures

In general, the frequency of seizures in patients treated with **PAXIL** is less than 0.1%. **PAXIL** should be discontinued in any patient who develops seizures.

Glaucoma

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

Electroconvulsive Therapy (ECT)

There is little clinical experience with concurrent administration of **PAXIL** and ECT. However, on rare occasions there have been reports of prolongation of ECT-induced seizures and/or secondary seizures in patients receiving SSRIs.

Hyponatremia

Hyponatremia has been reported rarely, predominantly in the elderly. Hyponatremia usually reverses with discontinuation of paroxetine.

Haemorrhage

Bleeding from the skin and mucous membranes (including gastrointestinal and gynaecological bleeding) has been reported following treatment with **PAXIL**. Therefore, **PAXIL** should be used with caution in patients who are being treated concomitantly with drugs that have a higher risk of bleeding, and in patients with a known tendency to bleed or in those with predisposing conditions (see *ADVERSE REACTIONS*). SSRIs may increase the risk of postpartum hemorrhage (see *Pregnancy and Breast-Feeding*).

Heart Conditions

In patients with cardiac conditions, the usual precautions should be observed.

QT Prolongation

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

PAXIL 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 Observed When Discontinuing **PAXIL** Treatment in Adults

In clinical studies in adults, adverse events observed upon discontinuation of treatment occurred in 30% of patients treated with **PAXIL** compared with 20% of those treated with placebo. The emergence of discontinuation symptoms does not mean the same as if the drug were addictive or dependent as it would be with a substance of abuse.

Dizziness, sensory disturbances (such as paresthesia, electric shaking sensations, and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, and diarrhea have been reported. These symptoms are usually mild to moderate; however, in some patients they may be of severe intensity. They usually occur in the first few days after discontinuing treatment, but very rarely there have been reports of these symptoms in patients who have inadvertently missed a dose. Ordinarily, these symptoms are self-limiting and under normal conditions remit within two weeks, although in some individuals they may be prolonged (two to three months or more). Therefore, it is recommended that upon discontinuation of treatment the dose of

PAXIL be gradually reduced over a period of several weeks or months, according to the patient's needs (see *"Discontinuation of **PAXIL**", Dosage and Administration*).

Sexual dysfunction

SSRIs can cause symptoms of sexual dysfunction (see *ADVERSE REACTIONS*). There have been reports of prolonged sexual dysfunction where symptoms have continued despite stopping SSRIs.

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

In clinical studies in children and adolescents, adverse events observed upon discontinuation of treatment occurred in 32% of patients treated with **PAXIL** compared with 24% of those treated with placebo. Events reported with discontinuation of **PAXIL** at least 2% of patients and occurring at least twice as often as placebo were: emotional instability (which included suicidal ideation, suicide attempt, mood disturbances, and tendency to tear), nervousness, dizziness, nausea and abdominal pain (see *ADVERSE REACTIONS*).

PAXIL liquid

PAXIL liquid contains the twilight yellow coloring agent FCF (FDC&C yellow No. 6), an azo dye that can cause allergic reactions.

PAXIL liquid contains methyl and propyl parahydroxybenzoate (parabens), both of which are known to cause hives, delayed-type reactions such as contact dermatitis and, rarely, immediate hypersensitivity reactions with bronchospasm.

In patients receiving **liquid PAXIL**, plasma concentrations of paroxetine may be influenced by gastric pH. In vitro data have demonstrated the need for an acidic environment for the release of the active drug from the liquid formulation, so it is possible that absorption is reduced in those patients who exhibit a high gastric pH. Therefore, caution is advised because, in certain situations, plasma concentrations of paroxetine may increase (e.g., after discontinuation of a proton pump inhibitor or histamine H2 receptor antagonist) or decrease (e.g., in patients with a high gastric pH who switch their tablet therapy to treatment with the liquid formulation).

Interactions

Serotonergic drugs

As with other SSRIs (selective serotonin reuptake inhibitors), coadministration with serotonergic drugs may produce several 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**. Concomitant use of **PAXIL** 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** 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 **PAXIL** must be coadministered with a known inhibitor of drug-metabolizing enzymes, doses at the lower end of the range should be considered. Adjustment of the starting dose is not considered necessary when the drug must be co-administered with known inducers of drug-metabolizing enzymes (e.g., carbamazepine, rifampicin, phenobarbital, phenytoin). Any subsequent dose adjustment should be guided by clinical effect (tolerability and efficacy).

Fosamprenavir/Ritonavir

Coadministration of fosamprenavir/ritonavir with paroxetine significantly decreases paroxetine plasma concentrations. Any dose 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, the dose of procyclidine should be reduced.

Anticonvulsants

Carbamazepine, phenytoin, sodium valproate. Concomitant administration does not appear to exhibit 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 mivacurium and suxamethonium.

Inhibitory Potency of Paroxetine on the CYP2D6 Enzyme

As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of the CYP2D6 enzyme may result in elevated plasma concentrations of coadministered drugs that are metabolized by this enzyme. These include some 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 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 steady-state co-administration of paroxetine and terfenadine, a substrate of the CYP3A4 enzyme, revealed no effects of paroxetine on the pharmacokinetic parameters of terfenadine. A similar in vivo interaction study revealed no effects of paroxetine on the pharmacokinetic parameters of alprazolam and vice versa. Concurrent administration of paroxetine with terfenadine, alprazolam and other drugs that are substrates of the CYP3A4 enzyme would not be expected to pose a danger.

Drugs that Affect Gastric pH

In vitro data have shown that the dissociation of paroxetine, from the liquid oral formulation, is pH dependent. Therefore, drugs that alter gastric pH (such as proton pump inhibitors or histamine₂ receptor antagonists) are able to affect plasma concentrations of paroxetine in patients on therapy with the liquid oral formulation (see *WARNINGS and PRECAUTIONS*).

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 change in dosing regimen) by:

- foods
- Antacids
- digoxin
- Propranolol
- Alcohol: Paroxetine does not increase the impairment of mental and motor skills caused by alcohol, however, concomitant use of **PAXIL** and alcohol is not recommended.

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 demonstrated selective teratogenic or embryotoxic effects.

Epidemiological studies on the outcome of pregnancies in which maternal exposure to antidepressants in the first trimester of pregnancy has been followed have reported an increased risk of congenital malformations, particularly cardiovascular (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** only if the potential benefit outweighs the potential risk. If a decision is made to discontinue **PAXIL** treatment 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 **PAXIL** treatment in adults.

There have been reports of preterm birth in pregnant women exposed to paroxetine or other SSRIs, although a causal relationship with drug therapy has not 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.

Neonates should be observed if maternal use of **PAXIL** continues into late pregnancy, because there have been reports of complications from neonates exposed to **PAXIL** or other SSRIs in the late third trimester of pregnancy. However, a causal association with drug therapy has not been confirmed. Clinical findings reported include: respiratory distress, cyanosis, apnea, seizures, unstable temperature, feeding-related problems, vomiting, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremor, nervousness, irritability, lethargy, constant crying, and drowsiness. In some cases the reported symptoms were described as symptoms of discontinuation in neonates. In a majority of cases, complications were reported to arise either immediately or shortly (< 24 hours) after delivery.

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 1 to 2 per 1000 pregnancies).

Nursing

Small amounts of paroxetine are excreted in breast milk. In published studies, serum concentrations in breastfed infants were either undetectable (< 2 nanogram/mL) or very low (< 4 nanogram/mL). No signs of drug effects were observed in these infants. However, **PAXIL** 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 Vehicles and Operate Machinery

Clinical experience has shown that **treatment with PAXIL** is not associated with impairment of cognitive or psychomotor function. However, as with all psychoactive drugs, patients should be warned about their ability to drive vehicles and operate machinery.

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

Adverse Reactions

Some of the adverse events listed below may decrease in intensity and frequency with continued treatment and generally do not require discontinuation. Adverse drug reactions are listed below by organ system class and frequency. Frequencies are defined as: very common (1/10), common (1/100, < 1/10), uncommon (1/1000, < 1/100), rare (1/10000, < 1/10000), very rare (< 1/10000), including isolated reports. The frequencies of common and uncommon events were generally determined based on pooled safety data from a clinical study population of > 8000 patients treated with paroxetine and are mentioned as the excess frequency above that reported with placebo. Rare and very rare events were generally determined based on postmarketing data and refer to reporting rate, rather than true frequency. >>>>

Disorders of the Hemic and Lymphatic System

Uncommon abnormal bleeding, predominantly from 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 antidiuretic hormone (SI) secretion. ADH

Metabolic and Nutritional Disorders

Common increases in cholesterol concentrations, decreased appetite.
Rare hypонатremia.

Hypонатremia has been reported predominantly in the elderly and is sometimes due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Psychiatric Disorders

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

These symptoms could be due to the underlying disease.

Nervous System Disorders

Common dizziness, tremor, headache.

Uncommon extrapyramidal disorders.

Rare seizures, akathisia, restless legs syndrome (RLS).

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

There have sometimes been reports of extrapyramidal disorders, including orofacial dystonia, in patients 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.

Heart Disorders

Uncommon sinus tachycardia.

Vascular Disorders

Uncommon orthostatic hypotension.

Respiratory, Thoracic and Mediastinal Disorders

Common yawns.

Gastrointestinal Disorders

Very common nausea.

Common constipation, diarrhea, vomiting, dry mouth.

Very rare gastrointestinal bleeding.

Hepatobiliary disorders

Rare elevated liver enzymes.

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

Elevation of liver enzymes has been reported. Very rarely, postmarketing reports of liver events (such as hepatitis, sometimes associated with jaundice and/or liver failure) have also been received. If there is prolonged elevation of liver function test results, discontinuation of paroxetine should be considered.

Skin and Subcutaneous Tissue Disorders

Common sweating.

Uncommon rashes.

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.

Reproductive System and Breast Disorders

Very common sexual dysfunction.

Rare hyperprolactinemia/galactorrhea, menstrual disorders (including menorrhagia, metrorrhagia, and amenorrhea).

General Disorders and Problems at the Administration Site

Common asthenia, increased body weight.

Very rare peripheral edema.

Symptoms Observed Upon Discontinuation of Paroxetine Treatment

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

Uncommon agitation, nausea, tremor, confusion, sweating, diarrhea.

As with many psychoactive medicines, discontinuation of **PAXIL** (especially when done abruptly) may produce symptoms such as dizziness, sensory disturbances (including paresthesia, electric shivering sensations, and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, headache, tremor, confusion, diarrhea, and sweating. In most patients, these events are mild to moderate and self-limiting. No particular group of patients appears to be at increased risk for these symptoms; therefore, it is recommended that when **PAXIL** treatment is no longer required, discontinuation by dose reduction be carried out (see **DOSAGE AND ADMINISTRATION AND WARNINGS AND PRECAUTIONS**).

Adverse Events Reported in Pediatric Clinical Trials

In paediatric clinical studies the following adverse events were reported at least 2% of patients and occurred at least twice the frequency of placebo: emotional instability (including self-harm, suicidal thoughts, suicide attempts, crying and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia and agitation. Suicidal thoughts and suicide attempts were mainly observed in clinical studies of adolescents with Major Depressive Disorder. Hostility was particularly present in children with obsessive-compulsive disorder and especially in children younger than 12 years of age.

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

Overdose

Symptoms and Signs

Based on the available information it is clear that the drug has a wide margin of safety. Overdose attempts have been reported in patients taking up to 2000 mg alone, or in combination with other drugs, including alcohol. Experience with **PAXIL** in overdose has indicated that, in addition to the symptoms mentioned in Adverse Reactions, fever, blood pressure changes, involuntary muscle contractions, anxiety and tachycardia have been reported.

Occasionally events such as coma or electrocardiographic (ECG) changes have been reported and on very rare occasions a fatal outcome has been reported, but generally when **PAXIL** was taken in conjunction with other psychotropic drugs, with or without alcohol.

Treatment

No specific antidote is known.

Treatment should consist of the general measures employed in the management of overdose with any antidepressant. 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 (5hydroxytryptamine, 5HT) and its antidepressant action and efficacy in the treatment of obsessive-compulsive disorder (OCD) and panic disorder are considered to be related to the specific inhibition it produces of serotonin reuptake in neurons in the brain.

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

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

In a placebo-controlled study, the efficacy of **PAXIL** in the treatment of panic disorder has been maintained for at least one year.

Pharmacokinetics

Absorption

Steady-state systemic concentrations are reached 7 to 14 days after initiation of treatment and pharmacokinetics do not appear to change during long-term therapy.

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

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 **PAXIL**.

Elimination

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

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: Calcium phosphate (E341), sodium starch glycolate, magnesium stearate (E572).

Tablet coating: hydroxypropylmethylcellulose (E464), titanium dioxide (E171), polyethylene glycol and polysorbate 80 (E433). The coating of the 30 mg tablets also contains indigo carmine (E132).

Liquid: Potassium polacryline, dispersible cellulose (E460), propylene glycol, glycerol (E422), sorbitol (E420), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sodium citrate (E331), citric acid (E330), sodium saccharin (E954), natural orange flavor, natural lemon flavor, yellow color (E110, twilight yellow FCF (FD&C yellow no. 6)), defoamer silicone, purified water. For important information on some of these excipients, see Warnings and Precautions.

Shelf Life

The expiration date is indicated on the packaging.

Liquid: Use for a period of one month after opening for the first time.

Storage

Storage conditions are detailed on the packaging.

The suspension should not be frozen.

Nature and Content of the Container

Tablets: Aluminum honeycomb packaging, childproof aluminum honeycomb packaging or polypropylene bottles.

Liquid: Glass jars with childproof closure.

Incompatibilities

There are no known incompatibilities with **PAXIL** tablets or liquid.

Use and Management

Liquid Shake the bottle before use. Discard one month after opening.

Not all presentations are available in all countries.

Version

GDS 48/IPI 33

Issue date

December 08, 2021