HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PAXIL safely and effectively. See full prescribing information for PAXIL.

PAXIL (paroxetine) tablets, for oral use
PAXIL (paroxetine) oral suspension
Initial U.S. Approval: 1992

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

Increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. PAXIL is not approved for use in pediatric patients. (5.1, 8.4)

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Sexual Dysfunction (5.13) 9/2021

----------INDICATIONS AND USAGE----------
PAXIL is a selective serotonin reuptake inhibitor (SSRI) indicated in adults for the treatment of (1):

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Panic Disorder (PD)
- Social Anxiety Disorder (SAD)
- Generalized Anxiety Disorder (GAD)
- Posttraumatic Stress Disorder (PTSD)

----------DOSAGE AND ADMINISTRATION----------

- Shake oral suspension well before administration (2.1)
- Recommended starting and maximum daily dosage for MDD, OCD, PD, and PTSD: (2.2)

Indication	Starting Daily Dose	Maximum Daily Dose
MDD	20 mg	50 mg
OCD	20 mg	60 mg
PD	10 mg	60 mg
PTSD	20 mg	50 mg

- Recommended starting dosage for SAD and GAD is 20 mg daily. (2.3)
- Elderly patients, patients with severe renal impairment or severe hepatic impairment: Starting dosage is 10 mg daily. Maximum dosage is 40 mg daily. (2.4)
- When discontinuing PAXIL, reduce dosage gradually. (2.6, 5.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Extended-release tablets: 10 mg, scored; 20 mg, scored; 30 mg; and 40 mg tablets. (3)
- Oral suspension: 10 mg/5 mL. (3)

----------CONTRAINDICATIONS----------

- Concomitant use of monoamine oxidase inhibitors (MAOIs) or use within 14 days of discontinuing a MAOI. (4, 5.3, 7)
- Concomitant use of pimozide or thioridazine. (4, 5.3,7)
- Known hypersensitivity to paroxetine or to any of the inactive ingredients in PAXIL. (4)

----------WARNINGS and PRECAUTIONS----------

- *Serotonin Syndrome:* Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If occurs, discontinue PAXIL and initiate supportive measures. (5.2)
- *Embryofetal and Neonatal Toxicity:* Can cause fetal and neonatal harm. Increased risk of cardiovascular malformations with exposure during the first trimester. Exposure in late pregnancy may lead to an increased risk for persistent pulmonary hypertension of the newborn. (5.4, 8.1)
- *Increased Risk of Bleeding*: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, other antiplatelet drugs, warfarin, and other anticoagulant drugs may increase risk. (5.5)
- *Activation of Mania/Hypomania*: Screen patients for bipolar disorder. (5.6)
- *Seizures*: Use with caution in patients with seizure disorders. (5.8)
- *Angle-Closure Glaucoma*: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.9)
- *Sexual Dysfunction:* PAXIL may cause symptoms of sexual dysfunction. (5.13)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥5% and at least twice placebo) are abnormal ejaculation, , asthenia, constipation, decreased appetite, diarrhea, dizziness, dry mouth, female genital disorder, impotence, infection, insomnia, libido decreased, male genital disorder, nausea, nervousness, somnolence, sweating, tremor, yawn. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- *Drugs Highly Bound to Plasma Protein*: Monitor for adverse reactions and reduce dosage of PAXIL or other protein-bound drugs (e.g., warfarin) as warranted. (7)
- *Drugs Metabolized by CYP2D6*: Reduce dosage of drugs metabolized by CYP2D6 as warranted. (7)
- *Concomitant use with tamoxifen*: Consider use of an alternative antidepressant with little or no CYP2D6 inhibition. (5.11, 7)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy*: Can cause fetal and neonatal harm. Advise women of potential risk to the fetus. (8.1)
- *Nursing Mothers*: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2021

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.1)]*. PAXIL is not approved for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

PAXIL is indicated in adults for the treatment of:

- Major depressive disorder (MDD)
- Obsessive compulsive disorder (OCD)
- Panic disorder (PD)
- Social anxiety disorder (SAD)
- Generalized anxiety disorder (GAD)
- Posttraumatic stress disorder (PTSD)

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

Administer PAXIL as a single daily dose in the morning, with or without food.

Shake the oral suspension well before administration.

2.2 Recommended Dosage for MDD, OCD, PD, and PTSD

The recommended starting dosages and maximum dosages of PAXIL in patients with MDD, OCD, PD, and PTSD are presented in Table 1.

In patients with an inadequate response, increase dosage in increments of 10 mg per day at intervals of at least 1 week, depending on tolerability.

Table 1: Recommended Daily Dosage of PAXIL in Patients with MDD, OCD, PD, and PTSD

Indication	Starting Dose	Maximum Dose
MDD	20 mg	50 mg
OCD	20 mg	60 mg
PD	10 mg	60 mg
PTSD	20 mg	50 mg

2.3 Recommended Dosage for SAD and GAD

SAD

The starting and recommended dosage in patients with SAD is 20 mg daily. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a range of 20 mg to 60 mg daily. While the safety of PAXIL has been evaluated in patients with SAD at doses up to 60 mg daily, available information does not suggest any additional benefit for doses above 20 mg daily *[see Clinical Studies (14.4)]*.

GAD

The starting and recommended dosage in patients with GAD is 20 mg daily. In clinical trials the effectiveness of PAXIL in GAD was demonstrated in patients dosed in a range of 20 mg to 50 mg daily. There is not sufficient evidence to suggest a greater benefit to doses higher than 20 mg daily *[see Clinical Studies (14.5)]*.

In patients with an inadequate response, increase dosage in increments of 10 mg per day at intervals of at least 1 week, depending on tolerability.

2.4 Screen for Bipolar Disorder Prior to Starting PAXIL

Prior to initiating treatment with PAXIL or another antidepressant, screen patients for a personal or family history of bipolar disorder, mania, or hypomania *[see Warnings and Precautions (5.6)]*.

2.5 Recommended Dosage for Elderly Patients, Patients with Severe Renal Impairment, and Patients with Severe Hepatic Impairment

The recommended initial dosage is 10 mg per day for elderly patients, patients with severe renal impairment, and patients with severe hepatic impairment. Dosage should not exceed 40 mg/day.

2.6 Switching Patients to or From a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days must elapse between discontinuation of a monoamine oxidase inhibitor (MAOI and initiation of PAXIL. In addition, at least 14 days must elapse after stopping PAXIL before starting an MAOI antidepressant *[see Contraindications (4), Warnings and Precautions (5.2)]*.

2.7 Discontinuation of Treatment With PAXIL

Adverse reactions may occur upon discontinuation of PAXIL *[see Warnings and Precautions (5.7)]*. Gradually reduce the dosage rather than stopping PAXIL abruptly whenever possible.

3 DOSAGE FORMS AND STRENGTHS

PAXIL tablets are available as:

- 10 mg yellow, scored tablet engraved on the front with “PAXIL” and on the back with “10”.
- 20 mg pink, scored tablet engraved on the front with “PAXIL” and on the back with “20”.
- 30 mg blue tablet engraved on the front with “PAXIL” and on the back with “30”.
- 40 mg green tablet engraved on the front with “PAXIL” and on the back with “40”.

PAXIL oral suspension is available as:

- 10 mg/5 mL orange colored, orange flavored suspension in bottles containing 250 mL.

4 CONTRAINDICATIONS

PAXIL is contraindicated in patients:

- Taking, or within 14 days of stopping, MAOIs (including the MAOIs linezolid and intravenous methylene blue) because of an increased risk of serotonin syndrome *[see Warnings and Precautions (5.2), Drug Interactions (7)]*.
- Taking thioridazine because of risk of QT prolongation *[see Warnings and Precautions (5. 3) and Drug Interactions (7)]*
- Taking pimozide because of risk of QT prolongation *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.
- With known hypersensitivity (e.g., anaphylaxis, angioedema, Stevens-Johnson syndrome) to paroxetine or any of the inactive ingredients in PAXIL *[see Adverse Reactions (6.1), (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 2.

Table 2: Risk Differences of the Number of Patients with Suicidal Thoughts and Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts and Behaviors per 1,000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional cases
18-24 years old	5 additional cases
	Decreases Compared to Placebo
25-64 years old	1 fewer case
≥65 years old	6 fewer cases

PAXIL is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants

delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing PAXIL, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Serotonin Syndrome

SSRIs, including PAXIL, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs *[see Contraindications (4), Drug Interactions (7.1)]*. Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of PAXIL with MAOIs is contraindicated. In addition, do not initiate PAXIL in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking PAXIL discontinue PAXIL before initiating treatment with the MAOI *[see Contraindications (4), Drug Interactions (7)]*.

Monitor all patients taking PAXIL for the emergence of serotonin syndrome. Discontinue treatment with PAXIL and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of PAXIL with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

5.3 Drug Interactions Leading to QT Prolongation

The CYP2D6 inhibitory properties of paroxetine can elevate plasma levels of thioridazine and pimozide. Since thioridazine and pimozide given alone produce prolongation of the QTc interval and increase the risk of serious ventricular arrhythmias, the use of PAXIL is contraindicated in combination with thioridazine and pimozide *[see Contraindications (4), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

5.4 Embryofetal and Neonatal Toxicity

PAXIL can cause fetal harm when administered to a pregnant woman. Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of cardiovascular malformations. Exposure to paroxetine in late pregnancy may lead to an increased

risk for persistent pulmonary hypertension of the newborn (PPNH) and/or neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding.

If PAXIL is used during pregnancy, or if the patient becomes pregnant while taking PAXIL, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5.5 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including PAXIL, increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), other antiplatelet drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that interfere with serotonin reuptake have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the increased risk of bleeding associated with the concomitant use of PAXIL and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio.

5.6 Activation of Mania or Hypomania

In patients with bipolar disorder, treating a depressive episode with PAXIL or another antidepressant may precipitate a mixed/manic episode. During controlled clinical trials of PAXIL, hypomania or mania occurred in approximately 1% of PAXIL-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. Prior to initiating treatment with PAXIL, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.

5.7 Discontinuation Syndrome

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible *[see Dosage and Administration (2.7)]*.

During clinical trials of GAD and PTSD, gradual decreases in the daily dose by 10 mg/day at weekly intervals followed by 1 week at 20 mg/day was used before treatment was discontinued. The following adverse reactions were reported at an incidence of 2% or greater for PAXIL and were at least twice that reported for placebo: Abnormal dreams, paresthesia, and dizziness Adverse reactions have been reported upon discontinuation of treatment with PAXIL in pediatric patients. The safety and effectiveness of PAXIL in pediatric patients have not been established *[see Boxed Warning, Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.

5.8 Seizures

PAXIL tablets and oral suspension have not been systematically evaluated in patients with seizure disorders. Patients with history of seizures were excluded from clinical studies. During clinical studies, seizures occurred in 0.1% of patients treated with PAXIL. PAXIL should be prescribed with caution in patients with a seizure disorder. Discontinue PAXIL in any patient who develops seizures.

5.9 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including PAXIL may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Cases of angle-closure glaucoma associated with use of PAXIL have been reported. Avoid use of antidepressants, including PAXIL in patients with untreated anatomically narrow angles.

5.10 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs, including PAXIL. Cases with serum sodium lower than 110 mmol/L have been reported. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In patients with symptomatic hyponatremia, discontinue PAXIL and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with SSRIs *[see Use in Specific Populations (8.5)]*.

5.11 Reduction of Efficacy of Tamoxifen

Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced with concomitant use of PAXIL as a result of paroxetine's irreversible inhibition of CYP2D6 and lower blood levels of tamoxifen *[see Drug Interactions (7)]*. One study suggests that the risk may increase with longer duration of coadministration. However, other studies have failed to demonstrate such a risk. 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.

5.12 Bone Fracture

Epidemiological studies on bone fracture risk during exposure to some antidepressants, including SSRIs, have reported an association between antidepressant treatment and fractures. There are multiple possible causes for this observation, and it is unknown to what extent fracture risk is directly attributable to SSRI treatment.

5.13 Sexual Dysfunction

Use of SSRIs, including PAXIL, may cause symptoms of sexual dysfunction *[see Adverse Reactions (6.1)]*. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm. It is important for prescribers to inquire about sexual function prior to initiation of PAXIL and to inquire specifically about changes in sexual function during

treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

6 ADVERSE REACTIONS

The following adverse reactions are included in more detail in other sections of the prescribing information:

- Hypersensitivity reactions to paroxetine *[see Contraindications (4)]*
- Suicidal Thoughts and Behaviors *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Embryofetal and Neonatal Toxicity *[see Warnings and Precautions (5.4)]*
- Increased Risk of Bleeding *[see Warnings and Precautions (5.5)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.6)]*
- Discontinuation Syndrome *[see Warnings and Precautions (5.7)]*
- Seizures *[see Warnings and Precautions (5.8)]*
- Angle-closure Glaucoma *[see Warnings and Precautions (5.9)]*
- Hyponatremia *[see Warnings and Precautions (5.10)]*
- Bone Fracture *[see Warnings and Precautions (5.12)]*
- Sexual Dysfunction *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data for PAXIL are from:

- 6-week clinical trials in MDD patients who received PAXIL 20 mg to 50 mg once daily
- 12-week clinical trials in OCD patients who received PAXIL 20 mg to 60 mg once daily
- 10- to 12-week clinical trials in PD patients who received PAXIL 10 mg to 60 mg once daily
- 12-week clinical trials in SAD patients who received PAXIL 20 mg to 50 mg once daily
- 8-week clinical trials in GAD patients who received PAXIL 10 mg to 50 mg once daily
- 12-week clinical trials in PTSD patients who received PAXIL 20 mg to 50 mg once daily

Adverse Reactions Leading to Discontinuation

Twenty percent (1,199/6,145) of patients treated with PAXIL in clinical trials in MDD and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients treated with PAXIL in clinical trials in SAD, OCD, PD, GAD, and PTSD, respectively, discontinued treatment due to an adverse reaction. The most common adverse reactions (≥1%) associated with discontinuation (i.e., those adverse reactions associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo) are presented in Table 3:

Table 3: Adverse Reactions Reported as Leading to Discontinuation (≥1% of PAXIL-Treated Patients and Greater than Placebo) in MDD, OCD, PD, SAD, GAD, and PTSD Trials

	MDD		OCD		PD		SAD		GAD		PTSD	
	PAXIL %	Placebo %	PAXIL %	Placebo %	PAXIL %	Placebo %	PAXIL %	Placebo %	PAXIL %	Placebo %	PAXIL %	Placebo %
CNS												
Somnolence	2.3	0.7	—		1.9	0.3	3.4	0.3	2.0	0.2	2.8	0.6
Insomnia	—	—	1.7	0	1.3	0.3	3.1	0			—	—
Agitation	1.1	0.5	—								—	—
Tremor	1.1	0.3	—				1.7	0			1.0	0.2
Anxiety	—	—	—				1.1	0			—	—
Dizziness	—	—	1.5	0			1.9	0	1.0	0.2	—	—
Gastroin-testinal												
Constipation	—		1.1	0							—	—
Nausea	3.2	1.1	1.9	0	3.2	1.2	4.0	0.3	2.0	0.2	2.2	0.6
Diarrhea	1.0	0.3	—									
Dry mouth	1.0	0.3	—								—	—
Vomiting	1.0	0.3	—				1.0	0			—	—
Flatulence							1.0	0.3			—	—
Other												
Asthenia	1.6	0.4	1.9	0.4			2.5	0.6	1.8	0.2	1.6	0.2
Abnormal Ejaculation[a]	1.6	0	2.1	0			4.9	0.6	2.5	0.5	—	—
Sweating	1.0	0.3	—				1.1	0	1.1	0.2	—	—
Impotence[a]	—		1.5	0							—	—
Libido Decreased							1.0	0			—	—

Where numbers are not provided the incidence of the adverse reactions in patients treated with PAXIL was not >1% or was not greater than or equal to 2 times the incidence of placebo.

[a.] Incidence corrected for gender.

Most Common Adverse Reactions

The most commonly observed adverse reactions associated with the use of PAXIL (incidence of 5% or greater and at least twice that for placebo) were:

MDD: Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

OCD: Nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

PD: Asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

SAD: Sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence.

GAD: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

PTSD: Asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence.

Adverse Reactions in Patients with MDD

Table 4 presents the adverse reactions that occurred at an incidence of 1% or more and greater than placebo in clinical trials of PAXIL-treated patients with MDD.

Table 4: Adverse Reactions (≥1% of PAXIL-Treated Patients and Greater than Placebo) in 6-Week Clinical Trials for MDD

Body System/ Adverse Reaction	**PAXIL (n = 421) %**	**Placebo (n = 421) %**
Body as a Whole		
Headache	18	17
Asthenia	15	6
Cardiovascular		
Palpitation	3	1
Vasodilation	3	1
Dermatologic		
Sweating	11	2
Rash	2	1
Gastrointestinal		
Nausea	26	9
Dry Mouth	18	12
Constipation	14	9
Diarrhea	12	8
Decreased Appetite	6	2

Flatulence	4	2
Oropharynx Disorder[a]	2	0
Dyspepsia	2	1
Musculoskeletal		
Myopathy	2	1
Myalgia	2	1
Myasthenia	1	0
Nervous System		
Somnolence	23	9
Dizziness	13	6
Insomnia	13	6
Tremor	8	2
Nervousness	5	3
Anxiety	5	3
Paresthesia	4	2
Libido Decreased	3	0
Drugged Feeling	2	1
Confusion	1	0
Respiration		
Yawn	4	0
Special Senses		
Blurred Vision	4	1
Taste Perversion	2	0
Urogenital System		
Ejaculatory Disturbance[b,c]	13	0
Other Male Genital Disorders[b,d]	10	0
Urinary Frequency	3	1
Urination Disorder[e]	3	0
Female Genital Disorders[b,f]	2	0

a. Includes mostly “lump in throat” and “tightness in throat.”

b. Percentage corrected for gender.

c. Mostly “ejaculatory delay.”

d. Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual dysfunction,” and “impotence.”

e. Includes mostly “difficulty with micturition” and “urinary hesitancy.”

f. Includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”

Adverse Reactions in Patients with OCD, PD, and SAD

Table 5 presents adverse reactions that occurred at a frequency of 2% or more in clinical trials in patients with OCD, PD, and SAD.

Table 5. Adverse Reactions (≥2% of PAXIL-Treated Patients and Greater than Placebo) in 10 to 12-Week Clinical Trials for OCD, PD, and SAD

	Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
Body System/Preferred Term	**PAXIL (n = 542) %**	**Placebo (n = 265) %**	**PAXIL (n = 469) %**	**Placebo (n = 324) %**	**PAXIL (n = 425) %**	**Placebo (n = 339) %**
Body as a Whole						
Asthenia	22	14	14	5	22	14
Abdominal Pain	-	-	4	3	—	—
Chest Pain	3	2	-	-	-	-
Back Pain	-	-	3	2	-	-
Chills	2	1	2	1	—	—
Trauma	—	—	—	—	3	1
Cardiovascular						
Vasodilation	4	1	—	—	—	—
Palpitation	2	0	—	—	—	—
Dermatologic						
Sweating	9	3	14	6	9	2
Rash	3	2	—	—	—	—
Gastrointestinal						
Nausea	23	10	23	17	25	7
Dry Mouth	18	9	18	11	9	3
Constipation	16	6	8	5	5	2
Diarrhea	10	10	12	7	9	6
Decreased Appetite	9	3	7	3	8	2
Dyspepsia	-	-	-	-		2
Flatulence	-	-	-	-	4	2
Increased Appetite	4	3	2	1	-	-
Vomiting	-	-	-	-	2	1
Musculoskeletal						
Myalgia	—	—	—	—	4	3
Nervous System						
Insomnia	24	13	18	10	21	16
Somnolence	24	7	19	11	22	5
Dizziness	12	6	14	10	11	7
Tremor	11	1	9	1	9	1
Nervousness	9	8	—	—	8	7
Libido Decreased	7	4	9	1	12	1

	Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
Body System/Preferred Term	**PAXIL (n = 542) %**	**Placebo (n = 265) %**	**PAXIL (n = 469) %**	**Placebo (n = 324) %**	**PAXIL (n = 425) %**	**Placebo (n = 339) %**
Agitation	—	—	5	4	3	1
Anxiety	—	—	5	4	5	4
Abnormal Dreams	4	1	—	—	—	—
Concentration Impaired	3	2	—	—	4	1
Depersonalization	3	0	—	—	—	—
Myoclonus	3	0	3	2	2	1
Amnesia	2	1	-	-	-	-
Respiratory System						
Rhinitis	-	-	3	0	-	-
Pharyngitis	—	—	—	—	4	2
Yawn	-	-	-	-	5	1
Special Senses						
Abnormal Vision	4	2	—	—	4	1
Taste Perversion	2	0	-	-	-	-
Urogenital System						
Abnormal Ejaculation[a]	23	1	21	1	28	1
Dysmenorrhea	—	—	—	—	5	4
Female Genital Disorder[a]	3	0	9	1	9	1
Impotence[a]	8	1	5	0	5	1
Urinary Frequency	3	1	2	0	—	—
Urination Impaired	3	0	—	—	—	—
Urinary Tract Infection	2	1	2	1	—	—

a. Percentage corrected for gender.

Adverse Reactions in Patients with GAD and PTSD

Table 6 presents adverse reactions that occurred at a frequency of 2% or more in clinical trials in patients with GAD and PTSD.

Table 6. Adverse Reactions (≥2% of PAXIL-Treated Patients and Greater than Placebo) in 8- to 12-Week Clinical Trials for GAD and PTSD[a]

	Generalized Anxiety	Posttraumatic Stress

Body System/ Preferred Term	Disorder		Disorder	
	Paxil (n= 735) %	Placebo (n = 529) %	PAXIL (n = 676) %	Placebo (n = 504) %
Body as a Whole				
Asthenia	14	6	12	4
Headache	17	14	---	---
Infection	6	3	5	4
Abdominal Pain			4	3
Trauma			6	5
Cardiovascular				
Vasodilation	3	1	2	1
Dermatologic				
Sweating	6	2	5	1
Gastrointestinal				
Nausea	20	5	19	8
Dry Mouth	11	5	10	5
Constipation	10	2	5	3
Diarrhea	9	7	11	5
Decreased Appetite	5	1	6	3
Vomiting	3	2	3	2
Dyspepsia	---	---	5	3
Nervous System				
Insomnia	11	8	12	11
Somnolence	15	5	16	5
Dizziness	6	5	6	5
Tremor	5	1	4	1
Nervousness	4	3	---	---
Libido Decreased	9	2	5	2
Abnormal Dreams			3	
Respiratory System				
Respiratory Disorder	7	5	---	---
Sinusitis	4	3	---	---
Yawn	4	---	2	<1
Special Senses				
Abnormal Vision	2	1	3	1
Urogenital System				
Abnormal Ejaculation[a]	25	2	13	2
Female Genital Disorder[a]	4	1	5	1
Impotence[a]	4	3	9	1

[a.] Percentage corrected for gender.

Dose Dependent Adverse Reactions

MDD

A comparison of adverse reaction rates in a fixed-dose study comparing PAXIL10 mg, 20 mg, 30 mg, and 40 mg once daily with placebo in the treatment of MDD revealed dose dependent adverse reactions, as shown in Table 7:

Table 7. Adverse Reactions (≥5% of PAXIL-Treated Patients and ≥ Twice the Rate of Placebo) (in a Dose-Comparison Trial in the Treatment of MDD

	Placebo	PAXIL			
		10 mg	20 mg	30 mg	40 mg
	n = 51	n = 102	n = 104	n = 101	n = 102
Body System/Preferred Term	%	%	%	%	%
Body as a Whole					
Asthenia	0.0	2.9	10.6	13.9	12.7
Dermatology					
Sweating	2.0	1.0	6.7	8.9	11.8
Gastrointestinal					
Constipation	5.9	4.9	7.7	9.9	12.7
Decreased Appetite	2.0	2.0	5.8	4.0	4.9
Diarrhea	7.8	9.8	19.2	7.9	14.7
Dry Mouth	2.0	10.8	18.3	15.8	20.6
Nausea	13.7	14.7	26.9	34.7	36.3
Nervous System					
Anxiety	0.0	2.0	5.8	5.9	5.9
Dizziness	3.9	6.9	6.7	8.9	12.7
Nervousness	0.0	5.9	5.8	4.0	2.9
Paresthesia	0.0	2.9	1.0	5.0	5.9
Somnolence	7.8	12.7	18.3	20.8	21.6
Tremor	0.0	0.0	7.7	7.9	14.7
Special Senses					
Blurred Vision	2.0	2.9	2.9	2.0	7.8
Urogenital System					
Abnormal Ejaculation	0.0	5.8	6.5	10.6	13.0
Impotence	0.0	1.9	4.3	6.4	1.9
Male Genital Disorders	0.0	3.8	8.7	6.4	3.7

OCD

In a fixed-dose study comparing placebo and PAXIL 20 mg, 40 mg, and 60 mg in the treatment of OCD, there was no clear relationship between adverse reactions and the dose of PAXIL to which patients were assigned.

PD

In a fixed-dose study comparing placebo and PAXIL 10 mg, 20 mg, and 40 mg in the treatment of PD, the following adverse reactions were shown to be dose-dependent: asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation.

SAD

In a fixed-dose study comparing placebo and PAXIL 20 mg, 40 mg and 60 mg in the treatment of SAD, for most of the adverse reactions, there was no clear relationship between adverse reactions and the dose of PAXIL to which patients were assigned.

GAD

In a fixed-dose study comparing placebo and PAXIL 20 mg and 40 mg in the treatment of GAD, the following adverse reactions were shown to be dose-dependent: asthenia, constipation, and abnormal ejaculation.

PTSD

In a fixed-dose study comparing placebo and PAXIL 20 mg and 40 mg in the treatment of PTSD, the following adverse reactions were shown to be dose-dependent: impotence and abnormal ejaculation.

Male and Female Sexual Dysfunction

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of SSRI treatment. However, reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and healthcare providers may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in labeling may underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in males and females with MDD, OCD, PD, SAD, GAD, and PTSD are displayed in Table 8.

Table 8. Adverse Reactions Related to Sexual Dysfunction in Patients Treated with PAXIL in Clinical Trials of MDD, OCD, PD, SAD, GAD, and PTSD

	PAXIL	Placebo
n (males)	**1446**	**1042**
	%	**%**
Decreased Libido	6 to15	0 to 5
Ejaculatory Disturbance	13 to 28	0 to 2
Impotence	2 to 9	0 to 3
n (females)	**1822**	**1340**
	%	**%**
Decreased Libido	0 to 9	0 to 2
Orgasmic Disturbance	2 to 9	0 to 1

PAXIL treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

Hallucinations

In pooled clinical trials of PAXIL, hallucinations were observed in 0.2% of PAXIL-treated patients compared to 0.1% of patients receiving placebo.

Less Common Adverse Reactions

The following adverse reactions occurred during the clinical studies of PAXIL and are not included elsewhere in the labeling.

Adverse reactions are categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse reactions are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare adverse reactions are those occurring in fewer than 1/1,000 patients.

Body as a Whole

Infrequent: Allergic reaction, chills, face edema, malaise, neck pain; *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

Cardiovascular System

Frequent: Hypertension, tachycardia; *infrequent:* Bradycardia, hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* Angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor,

phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System
Infrequent: Bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, abnormal liver function tests, rectal hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

Endocrine System
Rare: Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems
Infrequent: Anemia, leukopenia, lymphadenopathy, purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional
Frequent: Weight gain; infrequent: Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; rare: Alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System
Frequent: Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:* Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

Nervous System
Frequent: Emotional lability, vertigo; *infrequent:* Abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive

reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome.

Respiratory System
Infrequent: Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration.

Skin and Appendages
Frequent: Pruritus; *infrequent:* Acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis; herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses
Frequent: Tinnitus; *infrequent:* Abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect.

Urogenital System
Infrequent: Amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

6.2 Postmarketing Experience

The following reactions have been identified during post approval use of PAXIL. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, syndrome of inappropriate ADH secretion, prolactinemia and galactorrhea; extrapyramidal symptoms which

have included akathisia, bradykinesia, cogwheel rigidity, oculogyric crisis which has been associated with concomitant use of pimozide; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes), hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), vasculitic syndromes (such as Henoch-Schönlein purpura), and premature births in pregnant women. There has been a case report of severe hypotension when PAXIL was added to chronic metoprolol treatment.

7 DRUG INTERACTIONS

Table 9 presents clinically significant drug interactions with PAXIL.

Table 9 : Clinically Significant Drug Interactions with PAXIL

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	The concomitant use of SSRIs, including PAXIL, and MAOIs increases the risk of serotonin syndrome.
Intervention	PAXIL is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue *[see Dosage and Administration (2.5), Contraindications (4), Warnings and Precautions (5.2)]*.
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Pimozide and Thioridazine	
Clinical Impact	Increased plasma concentrations of pimozide and thioridazine, drugs with a narrow therapeutic index, may increase the risk of QTc prolongation and ventricular arrhythmias.
Intervention	PAXIL is contraindicated in patients taking pimozide or thioridazine *[see Contraindications (4)]*.
Other Serotonergic Drugs	
Clinical Impact	The concomitant use of serotonergic drugs with PAXIL increases the risk of serotonin syndrome.
Intervention	Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of PAXIL and/or concomitant serotonergic drugs *[see Warnings and Precautions (5.2)]*.
Examples	other SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort
Drugs that Interfere with Hemostasis (antiplatelet agents and anticoagulants)	
Clinical Impact	The concurrent use of an antiplatelet agent or anticoagulant with PAXIL may potentiate the risk of bleeding.

Intervention	Inform patients of the increased risk of bleeding associated with the concomitant use of PAXIL and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio *[see Warnings and Precautions (5.5)]*.
Examples	aspirin, clopidogrel, heparin, warfarin
Drugs Highly Bound to Plasma Protein	
Clinical Impact	PAXIL is highly bound to plasma protein. The concomitant use of PAXIL with another drug that is highly bound to plasma protein may increase free concentrations of PAXIL or other tightly-bound drugs in plasma.
Intervention	Monitor for adverse reactions and reduce dosage of PAXIL or other protein-bound drugs as warranted.
Examples	warfarin
Drugs Metabolized by CYP2D6	
Clinical Impact	PAXIL is a CYP2D6 inhibitor *[see Clinical Pharmacology (12.3)]*. The concomitant use of PAXIL with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate.
Intervention	Decrease the dosage of a CYP2D6 substrate if needed with concomitant PAXIL use. Conversely, an increase in dosage of a CYP2D6 substrate may be needed if PAXIL is discontinued.
Examples	propafenone, flecainide, atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine, risperidone.
Tamoxifen	
Clinical Impact	Concomitant use of tamoxifen with PAXIL may lead to reduced plasma concentrations of the active metabolite (endoxifen) and reduced efficacy of tamoxifen
Intervention	Consider use of an alternative antidepressant with little or no CYP2D6 inhibition *[see Warnings and Precautions (5.11)]*.
Fosamprenavir/Ritonavir	
Clinical Impact	Co-administration of fosamprenavir/ritonavir with PAXIL significantly decreased plasma levels of PAXIL.
Intervention	Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.4)]*

Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of congenital malformations, particularly cardiovascular malformations. If paroxetine is used during pregnancy, or if the patient becomes pregnant while taking paroxetine, advise the patient of the potential hazard to the fetus.

Clinical Considerations

Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant *[see Warnings and Precautions (5.7)]*. For

- A study based on Swedish national registry data demonstrated that infants exposed to paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular malformations (2% risk in paroxetine-exposed infants) compared to the entire registry population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No increase in the risk of overall congenital malformations was seen in the paroxetine-exposed infants. The cardiac malformations in the paroxetine-exposed infants were primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in severity from those that resolve spontaneously to those which require surgery.
- A separate retrospective cohort study from the United States (United Healthcare data) evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine (risk of 1.5%) compared to other antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study also suggested an increased risk of overall major congenital malformations including cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8).
- Two large case-control studies using separate databases, each with >9,000 birth defect cases and >4,000 controls, found that maternal use of paroxetine during the first trimester of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow tract obstructions. In one study the OR was 2.5 (95% confidence interval, 1.0 to 6.0, 7 exposed infants) and in the other study the OR was 3.3 (95% confidence interval, 1.3 to 8.8, 6 exposed infants).

Other studies have found varying results as to whether there was an increased risk of overall, cardiovascular, or specific congenital malformations. A meta-analysis of epidemiological data over a 16-year period (1992 to 2008) on first trimester paroxetine use in pregnancy and congenital malformations included the above-noted studies in addition to others (n = 17 studies that included overall malformations and n = 14 studies that included cardiovascular malformations; n = 20 distinct studies). While subject to limitations, this meta-analysis suggested

an increased occurrence of cardiovascular malformations (prevalence odds ratio [POR] 1.5; 95% confidence interval 1.2 to 1.9) and overall malformations (POR 1.2; 95% confidence interval 1.1 to 1.4) with paroxetine use during the first trimester. It was not possible in this meta-analysis to determine the extent to which the observed prevalence of cardiovascular malformations might have contributed to that of overall malformations, nor was it possible to determine whether any specific types of cardiovascular malformations might have contributed to the observed prevalence of all cardiovascular malformations.

Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant *[see Warnings and Precautions (5.7)]*. For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options *[see Warnings and Precautions (5.4)]*.

Treatment of Pregnant Women During Their Third Trimester: Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), including PAXIL, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

Exposure to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy.

There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment. A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy. The women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Animal Findings

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 6 (rat) and less than 2 (rabbit) times the maximum recommended human dose (MRHD – 75 mg) on an mg/m^2 basis. These studies have revealed no evidence of developmental effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day which is than the MRHD on an mg/m^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

8.3 Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from PAXIL, a decision should be made whether to discontinue nursing infants or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of PAXIL in pediatric patients have not been established *[see Box Warning]*. Effectiveness was not demonstrated in three placebo-controlled trials in 752 PAXIL-treated pediatric patients with MDD.

Antidepressants increase the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.1)]*. Decreased appetite and weight loss have been observed in association with the use of SSRIs.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse reactions were reported in at least 2% of pediatric patients treated with PAXIL and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Adverse reactions upon discontinuation of treatment with PAXIL in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients and at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain .

8.5 Geriatric Use

In premarketing clinical trials with PAXIL, 17% of patients treated with PAXIL (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended;, however, no overall differences in safety or effectiveness were observed between elderly and younger patients *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

SSRIs including PAXIL, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction *[see Warnings and Precautions (5.7)]*.

8.6 Renal and Hepatic Impairment

Increased plasma concentrations of paroxetine occur in patients with renal and hepatic impairment. The initial dosage of PAXIL should be reduced in patients with severe renal impairment and in patients with severe hepatic impairment *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The following have been reported with paroxetine tablet overdosage:

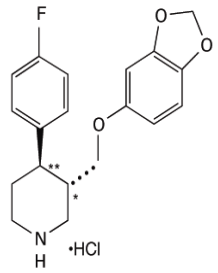
- Seizures, which may be delayed, and altered mental status including coma.
- Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.
- Serotonin syndrome (patients with a multiple drug overdosage with other proserotonergic drugs may have a higher risk).

Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a paroxetine overdose.

Consider contacting a Poison Center (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

PAXIL contains paroxetine hydrochloride, an SSRI. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \bullet HCl \bullet 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

PAXIL Tablets

PAXIL tablets are for oral administration. Each film-coated tablet contains 10 mg, 20 mg, 30 mg, or 40 mg of paroxetine equivalent to 11.1 mg, 22.2 mg, 33.3 mg or 44.4 mg of paroxetine hydrochloride, respectively.

Inactive ingredients consist of dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake.

PAXIL Oral Suspension

PAXIL oral suspension is for oral administration. Each 5 mL contains 10 mg of paroxetine equivalent to 11.1 mg of paroxetine hydrochloride.

Inactive ingredients consist of citric acid (anhydrous), FD&C yellow No. 6, flavorings, glycerin, methylparaben, microcrystalline cellulose and carboxymethylcellulose sodium, polacrilin potassium, propylene glycol, propylparaben, purified water, saccharin sodium, simethicone emulsion and sodium citrate (dihydrate).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of PAXIL in the treatment of MDD, SAD, OCD\, PD, GAD, and PTSD is unknown, but is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT).

12.2 Pharmacodynamics

Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake (SSRI) and has only very weak effects on norepinephrine and dopamine neuronal reuptake.

12.3 Pharmacokinetics

Nonlinearity in pharmacokinetics is observed with increasing doses of PAXIL.

In a meta-analysis of paroxetine from 4 studies done in healthy volunteers following multiple dosing of 20 mg/day to 40 mg/day, males did not exhibit a significantly lower C_{max} or AUC than females.

Absorption

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n = 15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min}, and $T_{½}$ were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

Paroxetine is equally bioavailable from the oral suspension and tablet.

Effect of Food
The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Distribution
Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Elimination
Metabolism
The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets daily for 30 days of PAXIL.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions *[see Drug Interactions (7)]*. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Excretion
Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Drug Interaction Studies

There are clinically significant, known drug interactions between paroxetine and other drugs *[see Drug Interactions (7)]*.

Figure 1. Impact of Paroxetine on the Pharmacokinetics of Co-Administered Drugs (log scale)

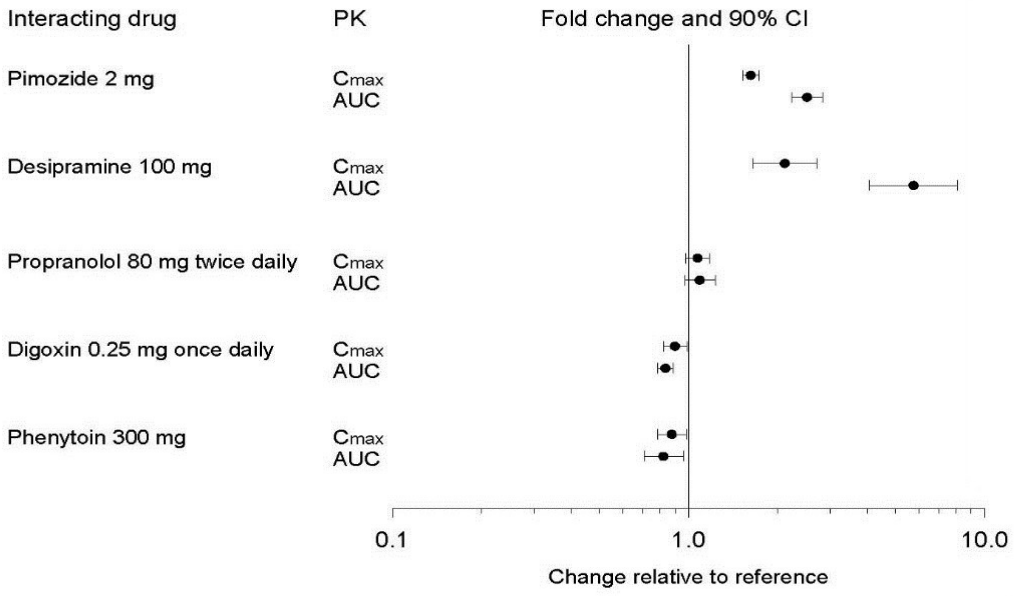
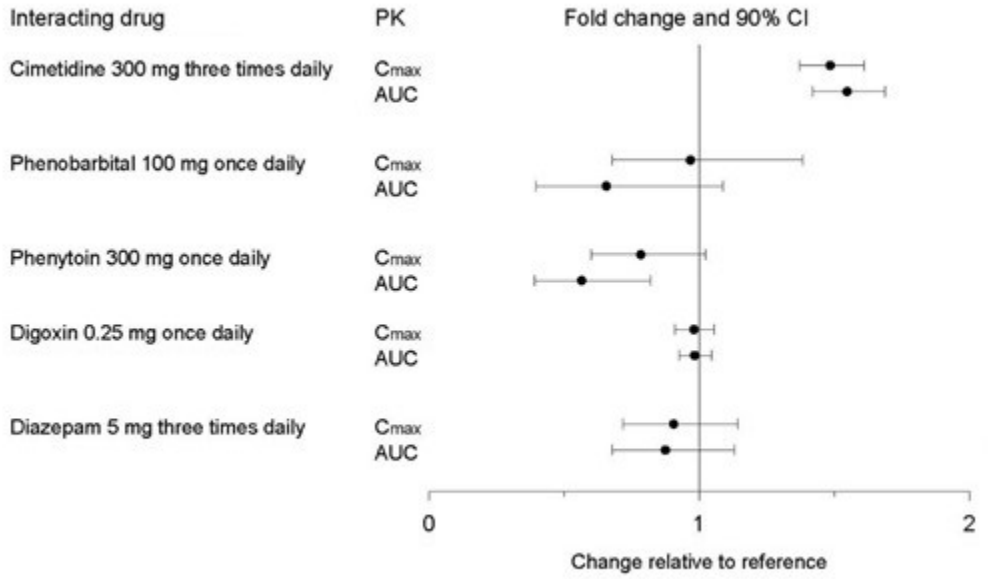


Figure 2. Impact of Co-Administered Drugs on the Pharmacokinetics of Paroxetine



Theophylline: Reports of elevated theophylline levels associated with PAXIL treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Drugs Metabolized by Cytochrome CYP3A4

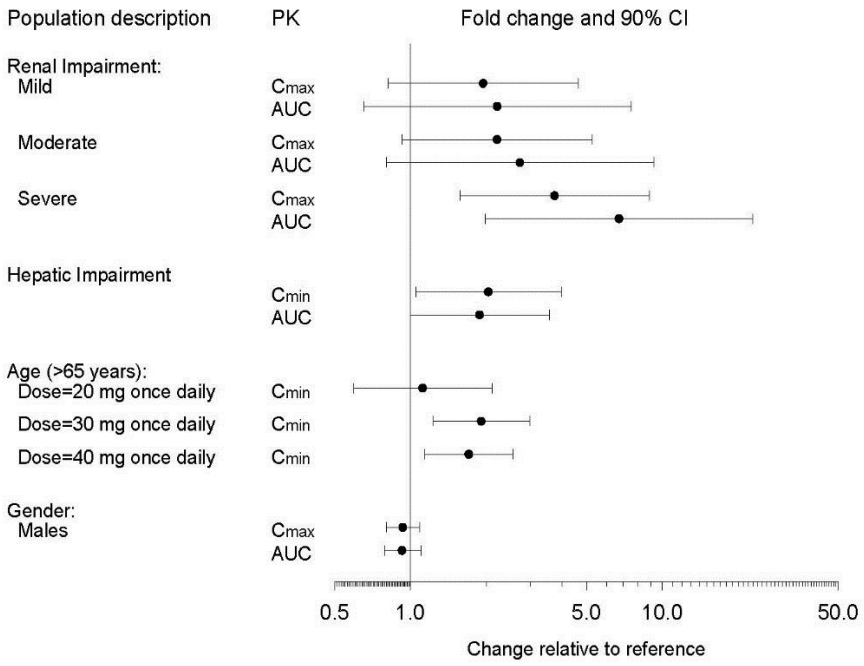
An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Paroxetine's extent of inhibition of CYP3A4 activity is not expected to be of clinical significance.

Specific Populations

The impact of specific populations on the pharmacokinetics of paroxetine are shown in Figure 3.

The recommended starting dosage and maximum dosage of PAXIL is reduced in elderly patients, patients with severe renal impairment, and patients with severe hepatic impairment *[see Dosage and Administration (2.4)]*.

Figure 3. Impact of Specific Population on the Pharmacokinetics of Paroxetine (log scale)



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.0 (mouse) and 3.2 (rat) times the MRHD of 75 mg on a mg/m^2 basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility

Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality during SSRI treatment, which may affect fertility in some men.

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.4 times the MRHD of 75 mg on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (8.2 and 4.1 times the MRHD of 75 mg on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

The efficacy of PAXIL as a treatment for major depressive disorder (MDD) has been established in 6 placebo-controlled studies of patients with MDD (aged 18 to 73). In these studies, PAXIL was shown to be statistically significantly more effective than placebo in treating MDD by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness. PAXIL was statistically significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor, and anxiety factor.

Long-term efficacy of PAXIL for treatment of MDD in outpatients was demonstrated in a randomized withdrawal study. Patients who responded to PAXIL (HDRS total score <8) during an initial 8-week open-label treatment phase were then randomized to continue PAXIL or placebo, for up to 1 year. Patients treated with PAXIL demonstrated a statistically significant lower relapse rate during the withdrawal phase (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

14.2 Obsessive Compulsive Disorder

The effectiveness of PAXIL in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. In study 1, a dose-range finding study, patients received fixed daily doses of PAXIL 20 mg, 40 mg, or 60 mg. Study 1 demonstrated that daily doses of PAXIL 40 mg and 60 mg are effective in the treatment of OCD. Patients receiving doses of PAXIL 40 mg and 60 mg experienced a mean reduction of approximately 6 and 7 points, respectively, on the YBOCS total score which was statistically significantly greater than the approximate 4-point reduction at 20 mg and a 3-point reduction in the placebo-treated patients. Study 2 was a flexible-dose study comparing PAXIL 20 mg to 60 mg daily with clomipramine 25 mg to 250 mg daily or placebo). In this study, patients receiving PAXIL experienced a mean reduction of approximately 7 points on the YBOCS total score, which was statistically significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impression (CGI) scale for Study 1.

Table 10: **Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1 in Patients with OCD**

Outcome Classification	Placebo (n = 74) %	PAXIL 20 mg (n = 75) %	PAXIL 40 mg (n = 66) %	PAXIL 60 mg (n = 66) %
Worse	14	7	7	3
No Change	44	35	22	19
Minimally Improved	24	33	29	34
Much Improved	11	18	22	24
Very Much Improved	7	7	20	20

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term efficacy of PAXIL for the treatment of OCD was established in a long-term extension to Study 1. Patients who responded to PAXIL during the 3-month double-blind phase and a 6-month extension on open-label PAXIL 20 mg to 60 mg daily were randomized to either PAXIL or placebo in a 6-month double-blind relapse prevention phase. Patients randomized to PAXIL were statistically significantly less likely to relapse than placebo-treated patients.

14.3 Panic Disorder

The effectiveness of PAXIL in the treatment of panic disorder (PD) was demonstrated in three 10- to 12-week multicenter, placebo-controlled studies of adult outpatients (Studies 1, 2, and 3). Patients had PD (DSM-IIIR), with or without agoraphobia. In these studies, PAXIL was shown to be statistically significantly more effective than placebo in treating PD by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 1 was a 10-week dose-range finding study; patients received fixed doses of PAXIL 10 mg, 20 mg, or 40 mg daily or placebo. A statistically significant difference from placebo was observed only for the PAXIL 40 mg daily group. At endpoint, 76% of patients receiving PAXIL 40 mg daily were free of panic attacks, compared to 44% of placebo-treated patients.

Study 2 was a 12-week flexible-dose study comparing PAXIL 10 mg to 60 mg daily and placebo. At endpoint, 51% of PAXIL-treated patients were free of panic attacks compared to 32% of placebo-treated patients.

Study 3 was a 12-week flexible-dose study comparing PAXIL 10 mg to 60 mg daily to placebo in patients concurrently receiving standardized cognitive behavioral therapy. At endpoint, 33% of the PAXIL-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo-treated patients.

In Studies 2 and 3, the mean PAXIL dose for completers at endpoint was approximately 40 mg daily.

Long-term efficacy of PAXIL in PD was demonstrated in an extension to Study 1. Patients who responded to PAXIL during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either PAXIL 10 mg, 20 mg, or 40 mg daily or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to PAXIL were statistically significantly less likely to relapse than placebo-treated patients.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

14.4 Social Anxiety Disorder

The effectiveness of PAXIL in the treatment of social anxiety disorder (SAD) was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies 1, 2, and 3) of adult outpatients with SAD (DSM-IV). In these studies, the effectiveness of PAXIL compared to placebo was evaluated on the basis of (1) the proportion of responders, as defined by a Clinical Global Impression (CGI) Improvement score of 1 (very much improved) or 2 (much improved), and (2) change from baseline in the Liebowitz Social Anxiety Scale (LSAS).

Studies 1 and 2 were flexible-dose studies comparing PAXIL 20 mg to 50 mg daily and placebo. PAXIL demonstrated statistically significant superiority over placebo on both the CGI Improvement responder criterion and the Liebowitz Social Anxiety Scale (LSAS). In Study 1, for patients who completed to week 12, 69% of PAXIL-treated patients compared to 29% of placebo-treated patients were CGI Improvement responders. In Study 2, CGI Improvement responders were 77% and 42% for the PAXIL- and placebo-treated patients, respectively.

Study 3 was a 12-week study comparing fixed doses of PAXIL 20 mg, 40 mg, or 60 mg daily with placebo. PAXIL 20 mg was statistically significantly superior to placebo on both the LSAS Total Score and the CGI Improvement responder criterion; there were trends for superiority over placebo for the PAXIL 40 mg and 60 mg daily dose groups. There was no indication in this study of any additional benefit for doses higher than 20 mg daily.

Subgroup analyses generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

14.5 Generalized Anxiety Disorder

The effectiveness of PAXIL in the treatment of generalized anxiety disorder (GAD) was demonstrated in two 8-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients with GAD (DSM-IV).

Study 1 was an 8-week study comparing fixed doses of PAXIL 20 mg or 40 mg daily with placebo. Doses of PAXIL 20 mg or 40 mg were both demonstrated to be statistically significantly superior to placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. There was not sufficient evidence in this study to suggest a greater benefit for the PAXIL 40 mg daily dose compared to the 20 mg daily dose.

Study 2 was a flexible-dose study comparing PAXIL 20 mg to 50 mg daily and placebo. PAXIL demonstrated statistically significant superiority over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score.

A third study, a flexible-dose study comparing PAXIL 20 mg to 50 mg daily to placebo, did not demonstrate statistically significant superiority of PAXIL over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

Subgroup analyses did not indicate differences in treatment outcomes as a function of race or gender. There were insufficient elderly patients to conduct subgroup analyses on the basis of age.

In a long-term trial, 566 patients meeting DSM-IV criteria for GAD, who had responded during a single-blind, 8-week acute treatment phase with PAXIL 20 mg to 50 mg daily, were randomized to continuation of PAXIL at their same dose, or to placebo, for up to 24 weeks of observation for relapse. Response during the single-blind phase was defined by having a decrease of ≥2 points compared to baseline on the CGI-Severity of Illness scale, to a score of ≤3. Relapse during the double-blind phase was defined as an increase of ≥2 points compared to baseline on the CGI-Severity of Illness scale to a score of ≥4, or withdrawal due to lack of efficacy. Patients continuing to receive PAXIL experienced a statistically significantly lower relapse rate over the subsequent 24 weeks compared to those receiving placebo.

14.6 Posttraumatic Stress Disorder

The effectiveness of PAXIL in the treatment of Posttraumatic Stress Disorder (PTSD) was demonstrated in two 12-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients who met DSM-IV criteria for PTSD. The mean duration of PTSD symptoms for the 2 studies combined was 13 years (ranging from 0.1 year to 57 years). The percentage of patients with secondary MDD or non-PTSD anxiety disorders in the combined 2 studies was 41% (356 out of 858 patients) and 40% (345 out of 858 patients), respectively. Study outcome was assessed by (1) the Clinician-Administered PTSD Scale Part 2 (CAPS-2) score and (2) the Clinical Global Impression-Global Improvement Scale (CGI-I). The CAPS-2 is a multi-item instrument that measures 3 aspects of PTSD with the following symptom clusters: Reexperiencing/intrusion, avoidance/numbing and hyperarousal. The 2 primary outcomes for each trial were (1) change from baseline to endpoint on the CAPS-2 total score (17 items), and (2) proportion of responders on the CGI-I, where responders were defined as patients having a score of 1 (very much improved) or 2 (much improved).

Study 1 was a 12-week study comparing fixed doses of PAXIL 20 mg or 40 mg daily to placebo. Doses of PAXIL 20 mg and 40 mg were demonstrated to be statistically significantly superior to placebo on change from baseline for the CAPS-2 total score and on proportion of responders on the CGI-I. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg daily dose compared to the 20 mg daily dose.

Study 2 was a 12-week flexible-dose study comparing PAXIL 20 mg to 50 mg daily to placebo. PAXIL was demonstrated to be significantly superior to placebo on change from baseline for the CAPS-2 total score and on proportion of responders on the CGI-I.

A third study, a flexible-dose study comparing PAXIL 20 mg to 50 mg daily to placebo, demonstrated PAXIL to be statistically significantly superior to placebo on change from baseline for CAPS-2 total score, but not on proportion of responders on the CGI-I.

The majority of patients in these trials were women (68% women: 377 out of 551 subjects in Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not indicate differences in treatment outcomes as a function of gender. There were an insufficient number of patients who were 65 years and older or were non-Caucasian to conduct subgroup analyses on the basis of age or race, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

PAXIL (paroxetine) tablets are oval shaped tablets supplied as:

Tablet Strength	Color	Engraved Descriptors	Package Configuration	NDC Number
10 mg	yellow	Scored, “PAXIL” on front and “10” on back	Bottles of 30	NDC 60505-4517-3
20 mg	pink	Scored, “PAXIL” on front and “20” on back	Bottles of 30	NDC 60505-4518-3
30 mg	blue	“PAXIL” on front and “30” on back	Bottles of 30	NDC 60505-4519-3
40 mg	green	“PAXIL” on front and “40” on back	Bottles of 30	NDC 60505-4520-3

Store tablets between 15° and 30°C (59° and 86°F).

PAXIL (paroxetine) oral suspension is supplied as:

Strength	Color/Flavor	Package Configuration	NDC Number
10 mg/5 mL	Orange/orange	Bottles containing 250 mL	NDC 60505-0402-5

Store suspension at or below 25°C (77°F)

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors
Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down, and instruct them to report such symptoms to the healthcare provider *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Serotonin Syndrome
Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of PAXIL with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, St. John’s Wort, and with drugs that

impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid). Instruct patients to contact their health care provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome *[see Warnings* and *Precautions (5.2), Drug Interactions (7)]*.

Concomitant Medications
Advise patients to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for drug-drug interactions *[see Warning and Precautions (5.3), Drug Interactions (7)]*.

Increased Risk of Bleeding
Inform patients about the concomitant use of PAXIL with aspirin, NSAIDs, other antiplatelet drugs, warfarin, or other anticoagulants because the combined use has been associated with an increased risk of bleeding. Advise patients to inform their health care providers if they are taking or planning to take any prescription or over-the counter medications that increase the risk of bleeding *[see Warnings and Precautions (5.5)]*.

Activation of Mania/Hypomania
Advise patients and their caregivers to observe for signs of activation of mania/hypomania and instruct them to report such symptoms to the healthcare provider *[see Warnings and Precautions (5.6)]*.

Discontinuation Syndrome
Advise patients not to abruptly discontinue PAXIL and to discuss any tapering regimen with their healthcare provider. Inform patients that adverse reactions can occur when PAXIL is discontinued *[See Warnings and Precautions (5.7)]*.

Sexual Dysfunction
Advise patients that use of PAXIL may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider *[see Warnings* and *Precautions (5.13)]*.

Administration Information for Oral Suspension
Instruct patients to shake the oral suspension well before administration *[see Dosage and Administration (2.1)]*.

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing *[see Adverse Reactions (6.1, 6.2)]*.

Embryo-Fetal Toxicity
Advise women of the potential risk to the fetus *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy because of the risk to the fetus.

Nursing

Advise women to notify their healthcare provider if they are breastfeeding an infant *[see Use In Specific Populations (8.3)]*.

Manufactured by: Apotex Inc**.** Toronto, Ontario M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL 33326

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MEDICATION GUIDE
PAXIL® (PAX-il)
(paroxetine)
tablets
oral suspension

What is the most important information I should know about PAXIL?

PAXIL can cause serious side effects, including:

- **Increased risk of suicidal thoughts or actions.** PAXIL and other antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger, especially within the **first few months of treatment or when the dose is changed**. **PAXIL is not for use in children.**
  - **Depression or other mental illnesses are the most important causes of suicidal thoughts and actions.**

How can I watch for and try to prevent suicidal thoughts and actions?

- Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts or feelings or if you develop suicidal thoughts or actions. This is very important when an antidepressant medicine is started or when the does is changed.
- Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts or feelings or if you develop suicidal thoughts or actions.
- Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider or get emergency medical help right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting aggressive or violent
- new or worse depression
- feeling agitated, restless, angry, or irritable
- an increase in activity and talking more than what is normal for you
- acting on dangerous impulses
- thoughts about suicide or dying
- new or worse anxiety or panic attacks
- trouble sleeping
- other unusual changes in behavior or mood

What is PAXIL?

PAXIL is a prescription medicine used in adults to treat:

- A certain type of depression called Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Panic Disorder (PD)
- Social Anxiety Disorder (SAD)
- Generalized Anxiety Disorder (GAD)
- Posttraumatic Stress Disorder (PTSD)

Do not take PAXIL if you:

- take a monoamine oxidase inhibitor (MAOI)
- have stopped taking an MAOI in the last 14 days
- are being treated with the antibiotic linezolid or the intravenous methylene blue
- are taking pimozide

- are taking thioridazine
- are allergic to paroxetine or any of the ingredients in PAXIL. See the end of this Medication Guide for a complete list of ingredients in PAXIL.

Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI or one of these medicines, including the antibiotic linezolid or intravenous methylene blue.

Do not start taking an MAOI for at least 14 days after you stop treatment with PAXIL.

Before taking PAXIL, tell your healthcare provider about all your medical conditions, including if you:

- have heart problems
- have or had bleeding problems
- have, or have a family history of, bipolar disorder, mania or hypomania
- have or had seizures or convulsions
- have glaucoma (high pressure in the eye)
- have low sodium levels in your blood
- have bone problems
- have kidney or liver problems
- are pregnant or plan to become pregnant. PAXIL may harm your unborn baby. Talk to your healthcare provider about the risks to your unborn baby if you take PAXIL during pregnancy. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with PAXIL.
- are breastfeeding or plan to breastfeed. PAXIL passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with PAXIL.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

PAXIL and some other medicines may affect each other causing possible serious side effects. PAXIL may affect the way other medicines work and other medicines may affect the way PAXIL works.

Especially tell your healthcare provider if you take:

- medicines used to treat migraine headaches called triptans
- tricyclic antidepressants
- fentanyl
- lithium
- tramadol
- tryptophan
- buspirone
- amphetamines
- St. John's Wort
- medicines that can affect blood clotting such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin
- diuretics
- tamoxifen
- medicines used to treat mood, anxiety, psychotic, or thought disorders, including selective serontonin reuptake (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

Ask your healthcare provider if you are not sure if you are taking any of these medicines. Your healthcare provider can tell you if it is safe to take PAXIL with your other medicines.

Do not start or stop any other medicines during treatment with PAXIL without talking to your healthcare provider first. Stopping PAXIL suddenly may cause you to have serious side effects. See, **"What are the possible side effects of PAXIL?"**

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take PAXIL?

- Take PAXIL exactly as prescribed. Your healthcare provider may need to change the dose of PAXIL until it is the right dose for you.
- Take PAXIL 1 time each day in the morning.
- PAXIL may be taken with or without food.
- If you are taking PAXIL oral suspension, shake the suspension well before taking.
- If you take too much PAXIL, call your poison control center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are possible side effects of PAXIL?

PAXIL can cause serious side effects, including:

- See, **"What is the most important information I should know about PAXIL?"**
- **Serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when you take PAXIL with certain other medicines. See, "Who should not take PAXIL?" **Call your healthcare provider or go to the nearest hospital emergency room right away** if you have any of the following signs and symptoms of serotonin syndrome:
  - o agitation
  - o seeing or hearing things that are not real (hallucinations)
  - o confusion
  - o coma
  - o fast heart beat
  - o changes in blood pressure
  - o dizziness
  - o sweating
  - o flushing
  - o high body temperature (hyperthermia)
  - o shaking (tremors), stiff muscles, or muscle twitching
  - o loss of coordination
  - o seizures
  - o nausea, vomiting, diarrhea
- **Eye problems (angle-closure glaucoma).** PAXIL may cause a type of eye problem called angle-closure glaucoma in people with certain other eye conditions. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are. Call your healthcare provider if you have eye pain, changes in your vision, or swelling or redness in or around the eye**.**
- **Medicine interactions.** Taking PAXIL with certain other medicines including thioridazine and pimozide may increase the risk of developing a serious heart problem called QT prolongation**.**
- **Seizures (convulsions).**
- **Manic episodes.** Manic episodes may happen in people with bipolar disorder who take PAXIL. Symptoms may include:
  - o greatly increased energy
  - o racing thoughts
  - o unusually grand ideas
  - o talking more or faster than usual
  - o severe problems sleeping
  - o reckless behavior
  - o excessive happiness or irritability
- **Discontinuation syndrome.** Suddenly stopping PAXIL may cause you to have serious side effects. Your healthcare provider may want to decrease your dose slowly. Symptoms may include:
  - o nausea
  - o sweating
  - o changes in your mood
  - o irritability and agitation
  - o electric shock feeling (paresthesia)
  - o tremor
  - o anxiety
  - o confusion
  - o tiredness
  - o problems sleeping
  - o hypomania
  - o ringing in your ears (tinnitus)

o dizziness o headache o seizures

- **Low sodium levels in your blood (hyponatremia).** Low sodium levels in your blood that may be serious and may cause death, can happen during treatment with PAXIL. Elderly people and people who take certain medicines may be at a greater risk for developing low sodium levels in your blood. Signs and symptoms may include:
  - o headache
  - o difficulty concentrating
  - o memory changes
  - o confusion
  - o weakness and unsteadiness on your feet which can lead to falls

  In more severe or more sudden cases, signs and symptoms include:
  - o seeing or hearing things that are not real (hallucinations)
  - o fainting
  - o seizures
  - o coma
  - o stopping breathing (respiratory arrest)
- **Abnormal bleeding.** Taking PAXIL with aspirin, NSAIDs, or blood thinners may increase this risk. Tell your healthcare provider about any unusual bleeding or bruising.
- **Bone fractures.**
- **Sexual problems (dysfunction).** Taking selective serotonin reuptake inhibitors (SSRIs), including PAXIL, may cause sexual problems.

  Symptoms in males may include:
  - o Delayed ejaculation or inability to have an ejaculation
  - o Decreased sex drive
  - o Problems getting or keeping an erection

  Symptoms in females may include:
  - o Decreased sex drive
  - o Delayed orgasm or inability to have an orgasm

  Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with PAXIL. There may be treatments your healthcare provider can suggest.

The most common side effects of PAXIL include:

- male and female sexual function problems
- constipation
- diarrhea
- dry mouth
- problems sleeping
- nervousness
- sweating
- yawning
- weakness (asthenia)
- decreased appetite
- dizziness
- infection
- nausea
- sleepiness
- shaking (tremor)

These are not all the possible side effects of PAXIL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PAXIL?

- Store PAXIL tablets between 59°F to 86°F (15°C to 30°C).

- Store PAXIL oral suspension at or below 77ºF (25ºC).

Keep PAXIL and all medicines out of the reach of children.

General information about the safe and effective use of PAXIL.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take PAXIL for a condition for which it was not prescribed. Do not give PAXIL to other people, even if they have the same symptoms that you have. It may harm them. You may ask your healthcare provider or pharmacist for information about PAXIL that is written for healthcare professionals.

What are the ingredients in PAXIL?

Active ingredient: paroxetine hydrochloride

Inactive ingredients:

Tablets: dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake

Oral suspension: citric acid (anhydrous), FD&C yellow No. 6, flavorings, glycerin, methylparaben, microcrystalline cellulose and carboxymethylcellulose sodium, polacrilin potassium, propylene glycol, propylparaben, purified water, saccharin sodium, simethicone emulsion and sodium citrate (dihydrate)

Manufactured by: Apotex Inc., Toronto, Ontario, Canada M9L 1T9
Manufactured for: Apotex Corp.: Weston, Florida USA 33326

For more information about PAXIL call 1-800-706-5575.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 9/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PAXIL CR safely and effectively. See full prescribing information for PAXIL CR.

PAXIL CR (paroxetine) extended-release tablets, for oral use
Initial U.S. Approval: 1992

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

Increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. PAXIL CR is not approved for use in pediatric patients. (5.1, 8.4)

RECENT MAJOR CHANGES

Warnings and Precautions, Sexual Dysfunction (5.13) 9/2021

INDICATIONS AND USAGE

PAXIL CR is a selective serotonin reuptake inhibitor (SSRI) indicated in adults for the treatment of (1):

- Major Depressive Disorder (MDD)
- Panic Disorder (PD)
- Social Anxiety Disorder (SAD)
- Premenstrual Dysphoric Disorder (PMDD)

DOSAGE AND ADMINISTRATION

- Swallow tablet whole; do not chew or crush. (2.1)
- Recommended starting and maximum daily dosage: (2.2, 2.3)

Indication	Starting Dose	Maximum Dose
MDD	25 mg/day	62.5 mg/day
PD	12.5 mg/day	75 mg/day
SAD	12.5 mg/day	37.5 mg/day
PMDD	12.5 mg/day	25 mg/day

- For PMDD, dose continuously or intermittently (luteal phase only). (2.3)
- If inadequate response to starting dosage, titrate in 12.5 mg per day increments once weekly. (2.2, 2.3)
- Elderly patients, patients with severe renal impairment or severe hepatic impairment: Starting dose is 12.5 mg per day. Do not exceed 50 mg per day for treatment of MDD and PD and 37.5 mg per day for treatment of SAD. (2.5)
- When discontinuing PAXIL CR, reduce dose gradually. (2.7)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 12.5 mg, 25 mg, and 37.5 mg tablets. (3)

CONTRAINDICATIONS

- Concomitant use of monoamine oxidase inhibitors (MAOIs) or use within 14 days of discontinuing a MAOIs. (4, 5.2, 7)
- Concomitant use of pimozide or thioridazine. (4, 5.3, 7)
- Known hypersensitivity to paroxetine or to any of the inactive ingredients in PAXIL CR. (4)

WARNINGS AND PRECAUTIONS

- *Serotonin Syndrome:* Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If occurs, discontinue PAXIL CR and initiate supportive measures. (5.2)
- *Embryofetal and Neonatal Toxicity:* Can cause fetal and neonatal harm. Increased risk of cardiovascular malformations for exposure during the first trimester. Exposure in late pregnancy may lead to an increased risk for persistent pulmonary hypertension (PPNH) of the newborn. (5.4, 8.1)
- *Increased Risk of Bleeding*: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, other antiplatelet drugs, warfarin, and other anticoagulant drugs may increase risk. (5.5)
- *Activation of Mania/Hypomania*: Screen patients for bipolar disorder. (5.6)
- *Seizures*: Use with caution in patients with seizure disorders. (5.8)
- *Angle-Closure Glaucoma*: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles, treated with antidepressants. (5.9)
- *Sexual Dysfunction*: PAXIL CR may cause symptoms of sexual dysfunction. (5.13)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and at least twice placebo) in placebo-controlled MDD, PD, SAD, and PMDD clinical trials:
abnormal ejaculation, abnormal vision, asthenia, constipation, decreased appetite, diarrhea, dizziness, dry mouth, female genital disorder, impotence, insomnia, libido decreased, nausea, somnolence, sweating, tremor. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Drugs Highly Bound to Plasma Protein*: Monitor for adverse reactions and reduce dosage of PAXIL CR or other protein-bound drugs (e.g., warfarin) as warranted. (7)
- *Drugs Metabolized by CYP2D6*: Reduce dosage of drugs metabolized by CYP2D6 as warranted. (7)
- *Concomitant use with Tamoxifen*: Consider use of an alternative antidepressant with little or no CYP2D6 inhibition. (5.11, 7)

USE IN SPECIFIC POPULATIONS

- *Pregnancy*: Can cause fetal and neonatal harm. Advise women of potential risk to the fetus. (5.4, 8.1)
- *Nursing Mothers*: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2021

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.1)]*. PAXIL CR is not approved for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

PAXIL CR is indicated in adults for the treatment of:

- Major depressive disorder (MDD)
- Panic disorder (PD)
- Social anxiety disorder (SAD)
- Premenstrual dysphoric disorder (PMDD)

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Administer PAXIL CR as a single daily dose in the morning, with or without food. Swallow tablets whole and do not chew or crush.

2.2 Dosage in Patients with Major Depressive Disorder, Panic Disorder, and Social Anxiety Disorder

The recommended initial dosage and maximum dosage of PAXIL CR in patients with MDD, PD, and SAD are presented in Table 1.

In patients with an inadequate response, dosage may be increased in increments of 12.5 mg per day at intervals of at least 1 week, depending on tolerability.

Table 1: Recommended Daily Dosage of PAXIL CR in Patients with MDD, PD, and SAD

Indication	Starting Dose	Maximum Dose
MDD	25 mg	62.5 mg
PD	12.5 mg	75 mg
SAD	12.5 mg	37.5 mg

2.3 Dosage in Patients with Premenstrual Dysphoric Disorder

The recommended starting dosage in women with PMDD is 12.5 mg per day. PAXIL CR may be administered either continuously (every day throughout the menstrual cycle) or intermittently (only during the luteal phase of the menstrual cycle, i.e., starting the daily dosage 14 days prior to the anticipated onset of menstruation and continuing through the onset of menses). Intermittent dosing is repeated with each new cycle.

In patients with an inadequate response, the dosage may be increased to the maximum recommended dosage of 25 mg per day, depending on tolerability. Institute dosage adjustments at intervals of at least 1 week.

2.4 Screen for Bipolar Disorder Prior to Starting PAXIL CR

Prior to initiating treatment with Paxil CR or another antidepressant, screen patients for a personal or family history of bipolar disorder, mania, or hypomania *[see Warnings and Precautions (5.6)]*.

2.5 Dosage Modifications for Elderly Patients, Patients with Severe Renal Impairment and Patients with Severe Hepatic Impairment

The recommended initial dose of PAXIL CR is 12.5 mg per day for elderly patients, patients with severe renal impairment, and patients with severe hepatic impairment. Reduce initial dose and increase up-titration intervals if necessary. Dosage should not exceed 50 mg per day for MDD or PD and should not exceed 37.5 mg per day for SAD *[see Use in Specific Populations (8.5, 8.6)]*.

2.6 Switching Patients to or from a Monoamine Oxidase Inhibitor Antidepressant

At least 14 days must elapse between discontinuation of an monoamine oxidase inhibitor (MAOI) antidepressant and initiation of PAXIL CR. In addition, at least 14 days must elapse after stopping PAXIL CR before starting an MAOI antidepressant *[see Contraindications (4), Warnings and Precautions (5.2)]*.

2.7 Discontinuation of Treatment with Paxil CR

Adverse reactions may occur upon discontinuation of PAXIL CR *[see Warnings and Precautions (5.6)]*. Gradually reduce the dosage rather than stopping Paxil CR abruptly whenever possible.

3 DOSAGE FORMS AND STRENGTHS

PAXIL CR extended-release tablets are available as:

- 12.5 mg yellow, round tablets, engraved on one side with “GSK” and engraved on the other side with “12.5”.
- 25 mg pink, round tablets, engraved on one side with “GSK” and engraved on the other side with “25”.
- 37.5 mg blue, round tablets, engraved on one side with “GSK” and engraved on the other side with “37.5”.

4 CONTRAINDICATIONS

PAXIL CR is contraindicated in patients:

- Taking, or within 14 days of stopping, MAOIs (including the MAOIs linezolid and intravenous methylene blue) because of an increased risk of serotonin syndrome *[See Warnings and Precautions (5.2), Drug Interactions (7)]*.
- Taking thioridazine because of risk of QT prolongation *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

- Taking pimozide because of risk of QT prolongation *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.
- With known hypersensitivity (e.g., anaphylaxis, angioedema, Stevens-Johnson syndrome) to paroxetine or to any of the inactive ingredients in PAXIL CR *[see Adverse Reactions (6.1, 6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 2.

Table 2: Risk Differences of the Number of Patients of Suicidal Thoughts and Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts and Behaviors per 1,000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing PAXIL CR, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Serotonin Syndrome

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs, including PAXIL CR, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants,

fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs *[see Contraindications (4), Drug Interactions (7.1)]*. Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of PAXIL CR with MAOIs is contraindicated. In addition, do not initiate PAXIL CR in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking PAXIL CR, discontinue PAXIL CR before initiating treatment with the MAOI *[see Contraindications (4), Drug Interactions (7.1)]*.

Monitor all patients taking PAXIL CR for the emergence of serotonin syndrome. Discontinue treatment with PAXIL CR and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of PAXIL CR with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

5.3 Drug Interactions Leading to QT Prolongation

The CYP2D6 inhibitory properties of paroxetine can elevate plasma levels of thioridazine and pimozide. Since thioridazine and pimozide given alone produce prolongation of the QTc interval and increase the risk of serious ventricular arrhythmias, the use of PAXIL CR is contraindicated in combination with thioridazine and pimozide *[see Contraindications (4), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

5.4 Embryofetal and Neonatal Toxicity

PAXIL CR can cause fetal harm when administered to a pregnant woman. Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of cardiovascular malformations. Exposure to paroxetine in late pregnancy may lead to an increased risk for persistent pulmonary hypertension of the newborn (PPNH) and/or neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding.

If PAXIL CR is used during pregnancy, or if the patient becomes pregnant while taking PAXIL CR, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5.5 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including PAXIL CR, increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), other antiplatelet drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association

between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that interfere with serotonin reuptake have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the increased risk of bleeding associated with the concomitant use of PAXIL CR and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio.

5.6 Activation of Mania or Hypomania

In patients with bipolar disorder, treating a depressive episode with PAXIL CR or another antidepressant may precipitate a mixed/manic episode. During controlled clinical trials of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. Prior to initiating treatment with PAXIL CR, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.

5.7 Discontinuation Syndrome

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible [*See Dosage and Administration (2.7)*].

Adverse reactions have been reported upon discontinuation of treatment with paroxetine in pediatric patients. The safety and effectiveness of PAXIL CR in pediatric patients have not been established *[see Boxed Warning, Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.

5.8 Seizures

PAXIL CR has not been systematically evaluated in patients with seizure disorders. Patients with history of seizures were excluded from clinical studies. PAXIL CR should be prescribed with caution in patients with a seizure disorder and should be discontinued in any patient who develops seizures.

5.9 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including PAXIL CR may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Cases of angle-closure glaucoma associated with use of paroxetine hydrochloride tablets have been reported. Avoid use of antidepressants, including PAXIL CR, in patients with untreated anatomically narrow angles.

5.10 Hyponatremia

Hyponatremia may occur as a result of treatment with SNRIs and SSRIs, including PAXIL CR. Cases with serum sodium lower than 110 mmol/L have been reported. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest,

and death. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In patients with symptomatic hyponatremia, discontinue PAXIL CR and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with SNRIs and SSRIs. *[see Use in Specific Populations (8.5)]*.

5.11 Reduction of Efficacy of Tamoxifen

Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced with concomitant use of paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 and lower blood levels of tamoxifen *[see Drug Interactions (7.3)]*. One study suggests that the risk may increase with longer duration of coadministration. However, other studies have failed to demonstrate such a risk. 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.

5.12 Bone Fracture

Epidemiological studies on bone fracture risk during exposure to some antidepressants, including SSRIs, have reported an association between antidepressant treatment and fractures. There are multiple possible causes for this observation, and it is unknown to what extent fracture risk is directly attributable to SSRI treatment.

5.13 Sexual Dysfunction

Use of SSRIs, including PAXIL CR, may cause symptoms of sexual dysfunction *[see Adverse Reactions (6.1)]*. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of PAXIL CR and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

6 ADVERSE REACTIONS

The following adverse reactions are included in more detail in other sections of the prescribing information:

- Hypersensitivity reactions to paroxetine *[see Contraindications (4)]*
- Suicidal Thoughts and Behaviors *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Embryofetal and Neonatal Toxicity *[see Warnings and Precautions (5.4)]*
- Increased Risk of Bleeding *[see Warnings and Precautions (5.5)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.6)]*
- Discontinuation Syndrome *[see Warnings and Precautions (5.7)]*

- Seizures *[see Warnings and Precautions (5.8)]*
- Angle-closure Glaucoma *[see Warnings and Precautions (5.9)]*
- Hyponatremia *[see Warnings and Precautions (5.10)]*
- Bone Fracture *[see Warnings and Precautions (5.12)]*
- Sexual Dysfunction *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data for PAXIL CR is from 11 short-term, placebo-controlled clinical trials including 3 studies in patients with major depressive disorder (MDD) (Studies 1, 2, and 3), 3 studies in patients with panic disorder (PD) (Studies 4, 5, and 6), 1 study in patients with social anxiety disorder (SAD) (Study 7), and 4 studies in female patients with premenstrual dysphoric disorder (PMDD) (Studies 8, 9, 10, and 11) *[see Clinical Studies (14)]*. These 11 trials included 1627 patients treated with Paxil CR.

- Studies 1 and 2 were 12-week studies that enrolled patients 18 to 65 years old who received PAXIL CR at doses ranging from 25 mg to 62.5 mg once daily. Study 3 was a 12-week study in patients 60 to 88 years old who received PAXIL CR at doses ranging from 12.5 mg to 50 mg once daily.

- Studies 4, 5, and 6 were 10-week studies in patients 19 to 72 years old who received PAXIL CR at doses ranging from 12.5 mg to 75 mg once daily.

- Study 7 was a 12-week study that enrolled adult patients who received PAXIL CR at doses ranging from 12.5 mg to 37.5 mg once daily.

- Studies 8, 9, and 10 were 12-week, placebo-controlled trials in female patients 18 to 46 years old who received PAXIL CR at doses of 12.5 mg or 25 mg once daily. Study 11 was a 12-week placebo-controlled trial in patients 18 to 46 years old who received PAXIL CR 2 weeks prior to the onset of menses (luteal phase dosing) at doses of 12.5 mg or 25 mg once daily.

<u>Adverse Reactions Leading to Discontinuation in Patients with MDD, PD, SAD, and PMDD</u>

In pooled studies in patients with MDD, PD and SAD, the most common adverse reactions leading to study withdrawal were: nausea (up to 4% of patients), asthenia, headache, depression, insomnia, and abnormal liver function tests (each occurring in up to 2% of patients), and dizziness, somnolence, and diarrhea (each occurring in up to 1% of patients).

In pooled studies for PMDD, the most common adverse reactions leading to study withdrawal were: nausea (occurring in up to 6% of patients), asthenia (occurring in up to 5% of patients), somnolence (occurring in up to 4% of patients), insomnia (occurring in approximately 2% of patients); and impaired concentration, dry mouth, dizziness, decreased appetite, sweating, tremor, yawn and diarrhea (occurring in less than or equal to 2% of patients).

Adverse Reactions in MDD, PD, and SAD

Table 3 presents the most common adverse reactions in PAXIL CR-treated patients (incidence ≥5% and greater than placebo within at least 1 of the indications) in controlled trials in patients with MDD, PD, and SAD.

Table 3. Adverse Reactions (≥5% of Patients Treated with PAXIL CR and Greater than Placebo) in 10 to 12 Week Studies of MDD, PD, and SAD

	MDD 18 to 65 year olds		**MDD ≥60 years old**		**Panic Disorder**		**Social Anxiety Disorder**	
Body System/ Adverse Reaction	PAXIL CR (N=212) %	Placebo (N=211) %	PAXIL CR (N=104) %	Placebo (N=109 %	PAXIL CR (N=444) %	Placebo (N=445) %	PAXIL CR (N=186) %	Placebo (N=184) %
Body as a Whole								
Headache	27	20	17	13	NA	NA	23	17
Asthenia	14	9	15	14	15	10	18	7
Abdominal Pain	7	4	-	-	6	4	5	4
Back Pain	5	3	-	-	NA	NA	4	1
Digestive System								
Nausea	22	10	-	-	23	17	22	6
Diarrhea	18	7	15	9	12	9	9	8
Dry Mouth	15	8	18	7	13	9	3	2
Constipation	10	4	13	5	9	6	5	2
Flatulence	6	4	-	-	NA	NA	NA	NA
Decreased Appetite		2	12	5	8	6	1	<1
Dyspepsia	NA	NA	13	10	NA	NA	2	<1
Musculoskeletal System								
Myalgia	NA	NA	-	-	5	3	NA	NA
Nervous System								
Somnolence	22	8	21	12	20	9	9	4
Insomnia	17	9	10	8	20	11	9	4
Dizziness	14	4	9	5	NA	NA	7	4
Libido Decreased	7	3	8	<1	9	4		1
Nervousness	NA	NA	-	-	8	7	NA	NA
Tremor	7	1	7	0	8	2	4	2
Anxiety	NA	NA	-	-	5	4	2	1
Respiratory System								
Sinusitis	NA	NA	-	-	8	5	NA	NA

Yawn		0	-	-	3	0	2	0
Skin and Appendages								
Sweating	6	2	10	<1	7	2	14	3
Special Senses								
Abnormal Vision[a]	5	1	-	-	3	<1	2	0
Urogenital System								
Abnormal Ejaculation[b,c]	26	1	17	3	27	3	15	1
Female Genital Disorder[b,d]	10	<1	-	-	7	1	3	0
Impotence[b]	5	3	9	3	10	1	9	0

Hyphen = the reaction listed occurred in <5% of patients treated with PAXIL CR
NA = the adverse reaction listed did not occur in this group of patients
[a] Mostly blurred vision
[b] Based on the number of males or females
[c] Mostly anorgasmia or delayed ejaculation
[d] Mostly anorgasmia or delayed orgasm

Other Adverse Reactions Observed During the Premarketing Evaluation of PAXIL CR

Adverse reactions from studies in MDD (not including Study 3 in elderly patients), PD, and SAD that occurred between 1% and 5% of patients treated with PAXIL CR and at a rate greater than in placebo-treated patients include:, allergic reaction, tachycardia, vasodilatation, hypertension, migraine, vomiting, weight loss, weight gain, hypertonia, paresthesia, agitation, confusion, myoclonus, concentration impaired, depression, rhinitis, cough increased, bronchitis, photosensitivity, eczema, taste perversion, UTI, menstrual disorder, urinary frequency, urination impaired, and vaginitis.

Adverse Reactions in Patients with PMDD

Table 4 displays adverse reactions that occurred (incidence of 5% or more and greater than placebo within at least 1 of the studies) in patients treated with PAXIL CR in Studies 8, 9, 10, and 11.

Table 4. Adverse Reactions (≥5% of Patients Treated with PAXIL CR and Greater than Placebo) in Pooled Studies PMDD (Studies 8, 9, 11), and in Study 10[a,b,c]

Body System/Adverse Reaction	% Reporting Adverse Reaction			
	Continuous Dosing Studies 8, 9, and 10		Luteal Phase Dosing Study 11	
	PAXIL CR (n = 681) %	Placebo (n = 349) %	PAXIL CR (n = 246) %	Placebo (n = 120) %
Body as a Whole				
Asthenia	17	6	15	4
Headache	15	12	NA	NA
Infection	6	4	NA	NA
Digestive System				
Nausea	17	7	18	2
Diarrhea	6	2	6	0
Constipation	5	1	2	<1
Nervous System				
Libido Decreased	12	5	9	6
Somnolence	9	2	3	<1
Insomnia	8	2	7	3
Dizziness	7	3	6	3
Tremor	4	<1	5	0
Skin and Appendages				
Sweating	7	<1	6	<1
Urogenital System				
Female Genital Disorders[c]	8	1	2	0

NA= the adverse reaction information is not available in this population.
[a] <1% means greater than zero and less than 1%.
[b] The luteal phase and continuous dosing PMDD trials were not designed for making direct comparisons between the 2 dosing regimens.
[c] Mostly anorgasmia or difficulty achieving orgasm.

Dose Dependent Adverse Reactions

Comparison of the incidence of adverse reactions (placebo vs. 12.5 mg PAXIL CR vs. 25 mg PAXIL CR) from studies 8, 9, 10 showed the following adverse reactions to be dose-related: Nausea, somnolence, sweating, dry mouth, dizziness, decreased appetite, tremor, impaired concentration, yawn, paresthesia, hyperkinesia, and vaginitis.

Male and Female Sexual Dysfunction

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of SSRI treatment. However, reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, in part because patients and healthcare providers may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in labeling may underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in the Studies 1 and 2 (nonelderly patients with MDD), 4, 5, 6, 7, 8, 9, 10, and 11 are presented in Table 5:

Table 5. Adverse Reactions Related To Sexual Dysfunction In Patients Treated With PAXIL CR in Pooled 10-12 Week Studies of MDD, PD, SAD, and PMDD

	Studies 1 and 2 %		Studies 4, 5, and 6 %		Study 7 %		Studies 8, 9, and 11 (Continuous Dosing) %		Study 10 (Luteal Phase Dosing) %	
	PAXIL CR	**Placebo**	**PAXIL CR**	**Placebo**	**PAXIL CR**	**Placebo**	**PAXIL CR**	**Placebo**	**PAXIL CR**	**Placebo**
n (males)	**78**	**78**	**162**	**194**	**88**	**97**	**NA**	**NA**	**NA**	**NA**
Decreased Libido	10	5	9	6	13	1	NA	NA	NA	NA
Abnormal ejaculation	26	1	27	3	15	1	NA	NA	NA	NA
Impotence	5	3	10	1%	9	0	NA	NA	NA	NA
n (females)	**134**	**133**	**282**	**251**	**98**	**87**	**681**	**349**	**246**	**120**
Decreased Libido	4	2	8	2	4	1	12	5	9	6
Orgasmic Disturbance	10	<1	7	1	3	0	8	1	2	0

NA = the adverse reaction listed did not occur in this group of patients.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

Less Common Adverse Reactions

The following adverse reactions occurred during the clinical studies of PAXIL CR and are not included elsewhere in the labeling.

Reactions are categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse reactions are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare reactions are those occurring in fewer than 1/1,000 patients.

Cardiovascular System: Infrequent was postural hypotension.

Hemic and Lymphatic System: Rare was thrombocytopenia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema and hypercholesteremia.

Nervous System: Infrequent were convulsion, akathisia, and manic reaction.

Psychiatric: Infrequent were hallucinations.

Skin and Appendages: Frequent was rash; infrequent was urticaria; rare was angioedema and erythema multiforme.

Urogenital System: Infrequent was urinary retention; rare was urinary incontinence.

6.2 Postmarketing Experience

The following reactions have been identified during post approval use of paroxetine. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion (SIADH), prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes), hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura).

7 DRUG INTERACTIONS

7.1 Clinically Significant Drug Interactions

Table 6 includes clinically significant drug interactions with PAXIL CR.

Table 6: Clinically Significant Drug Interactions with PAXIL CR

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	The concomitant use of SSRIs, including PAXIL CR, and MAOIs increases the risk of serotonin syndrome.
Intervention	PAXIL CR is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue *[see Dosage and Administration (2.6), Contraindications (4), Warnings and Precautions (5.2)]*.
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Pimozide and Thioridazine	
Clinical Impact	Increased plasma concentrations of pimozide and thioridazine, drugs with a narrow therapeutic index, may increase the risk of QTc prolongation and ventricular arrhythmias.
Intervention	PAXIL CR is contraindicated in patients taking pimozide or thioridazine *[see Contraindications (4)]*.
Other Serotonergic Drugs	
Clinical Impact	The concomitant use of serotonergic drugs with PAXIL CR increases the risk of serotonin syndrome.

Intervention	Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of PAXIL CR and/or concomitant serotonergic drugs *[see Warnings and Precautions (5.2)]*.
Examples	other SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort
Drugs that Interfere with Hemostasis (antiplatelet agents and anticoagulants)	
Clinical Impact	The concurrent use of an antiplatelet agent or anticoagulant with PAXIL CR may potentiate the risk of bleeding.
Intervention	Inform patients of the increased risk of bleeding associated with the concomitant use of PAXIL CR and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio *[see Warnings and Precautions (5.5)]*.
Examples	aspirin, clopidogrel, heparin, warfarin
Drugs Highly Bound to Plasma Protein	
Clinical Impact	PAXIL CR is highly bound to plasma protein. The concomitant use of PAXIL CR with another drug that is highly bound to plasma protein may increase free concentrations of PAXIL CR or other tightly-bound drugs in plasma.
Intervention	Monitor for adverse reactions and reduce dosage of PAXIL CR or other protein-bound drugs as warranted.
Examples	warfarin
Drugs Metabolized by CYP2D6	
Clinical Impact	PAXIL CR is a CYP2D6 inhibitor *[see Clinical Pharmacology (12.3)]*. The concomitant use of PAXIL CR with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate.
Intervention	Decrease the dosage of a CYP2D6 substrate if needed with concomitant PAXIL CR use. Conversely, an increase in dosage of a CYP2D6 substrate may be needed if PAXIL CR is discontinued.
Examples	propafenone, flecainide, atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine, risperidone.
Tamoxifen	
Clinical Impact	Concomitant use of tamoxifen with PAXIL CR may lead to reduced plasma concentrations of the active metabolite (endoxifen) and reduced efficacy of tamoxifen
Intervention	Consider use of an alternative antidepressant little or no CYP2D6 inhibition *[see Warnings and Precautions (5.11)]*.
Fosamprenavir/Ritonavir	

Clinical Impact	Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine.
Intervention	Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.14)]*

Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of congenital malformations, particularly cardiovascular malformations. If paroxetine is used during pregnancy, or if the patient becomes pregnant while taking paroxetine, advise the patient of the potential hazard to the fetus.

- A study based on Swedish national registry data demonstrated that infants exposed to paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular malformations (2% risk in paroxetine-exposed infants) compared to the entire registry population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No increase in the risk of overall congenital malformations was seen in the paroxetine-exposed infants. The cardiac malformations in the paroxetine-exposed infants were primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in severity from those that resolve spontaneously to those which require surgery.
- A separate retrospective cohort study from the United States (United Healthcare data) evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine (risk of 1.5%) compared to other antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study also suggested an increased risk of overall major congenital malformations including cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8).
- Two large case-control studies using separate databases, each with >9,000 birth defect cases and >4,000 controls, found that maternal use of paroxetine during the first trimester of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow tract obstructions. In one study the OR was 2.5 (95% confidence interval, 1.0 to 6.0, 7 exposed infants) and in the other study the OR was 3.3 (95% confidence interval, 1.3 to 8.8, 6 exposed infants).

Other studies have found varying results as to whether there was an increased risk of overall, cardiovascular, or specific congenital malformations. A meta-analysis of epidemiological data over a 16-year period (1992 to 2008) on first trimester paroxetine use in pregnancy and congenital malformations included the above-noted studies in addition to others (n = 17 studies that included overall malformations and n = 14 studies that included cardiovascular malformations; n = 20 distinct studies). While subject to limitations, this meta-analysis suggested an increased occurrence of cardiovascular malformations (prevalence odds ratio [POR] 1.5; 95% confidence interval 1.2 to 1.9) and overall malformations (POR 1.2; 95% confidence interval 1.1

to 1.4) with paroxetine use during the first trimester. It was not possible in this meta-analysis to determine the extent to which the observed prevalence of cardiovascular malformations might have contributed to that of overall malformations, nor was it possible to determine whether any specific types of cardiovascular malformations might have contributed to the observed prevalence of all cardiovascular malformations.

Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant *[see Warnings and Precautions (5.7)]*. For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options *[see Warnings and Precautions (5.4)]*.

Treatment of Pregnant Women During Their Third Trimester: Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), including PAXIL CR, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

Exposure to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy.

There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment *[see Dosage and Administration (2.5)]*. A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy. The women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 6 (rat) and less than 2 (rabbit) times the maximum recommended human dose (MRHD – 75 mg) on an mg/m^2 basis. These studies have revealed no evidence of malformations. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during

the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-thirteens of the MRHD on an mg/m^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

8.3 Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from PAXIL CR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of PAXIL CR in pediatric patients have not been established *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with immediate-release paroxetine, and effectiveness was not established in pediatric patients.

Decreased appetite and weight loss have been observed in association with the use of SSRIs.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse reactions were reported in at least 2% of pediatric patients treated with immediate-release paroxetine hydrochloride and at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Adverse reactions upon discontinuation of treatment with immediate-release paroxetine hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients and at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain.

8.5 Geriatric Use

SSRIs and SNRIs, including PAXIL CR, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction *[see Warnings and Precautions (5.9)]*.

In premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine treated patients (approximately 700) were 65 years or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; however, no overall differences in safety or effectiveness were observed between these subjects and younger subjects *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8.6 Renal and/or Hepatic Impairment

Increased plasma concentrations of paroxetine occur in patients with renal and hepatic impairment. The initial dosage should be reduced in patients with severe renal impairment and

patients with severe hepatic impairment *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The following have been reported with paroxetine tablet overdosage:

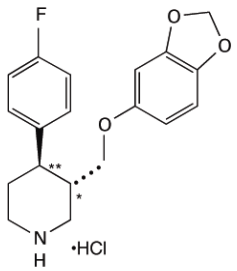
- Seizures, which may be delayed, and altered mental status including coma.
- Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.
- Serotonin syndrome (patients with a multiple drug overdosage with other proserotonergic drugs may have a higher risk).

Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a paroxetine overdose.

Consider contacting a Poison Center (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

PAXIL CR, contains paroxetine hydrochloride, an SSRI. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \bullet HCl \bullet 1/2H_2O$. The molecular weight is 374.8 g/mol (329.4 g/mol as free base). The structural formula of paroxetine hydrochloride is:



Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° C to 138°C and a solubility of 5.4 mg/mL in water.

PAXIL CR tablets are intended for oral administration. Each extended-release tablet contains 12.5 mg, 25 mg, or 37.5 mg paroxetine equivalent to 14.25 mg, 28.51 mg, or 42.76 mg of paroxetine hydrochloride, respectively. One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix.

Inactive ingredients consist of glyceryl behenate, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer type C, polyethylene glycols, polysorbate 80, polyvinylpyrrolidone, silicon dioxide, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate and the following colorants: D&C Red No. 30 aluminum lake (25 mg), D&C Yellow No. 10 aluminum lake (12.5 mg), FD&C Blue No. 2 aluminum lake (37.5 mg), FD&C Yellow No. 6

aluminum lake (12.5 mg), red ferric oxide (25 mg) and Yellow ferric oxide (12.5 mg and 37.5 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of paroxetine in the treatment of major depressive disorder (MDD), panic disorder (PD), social anxiety disorder (SAD), and premenstrual dysphoric disorder (PMDD) is unknown, but is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-HT).

12.2 Pharmacodynamics

Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake (SSRI) and has only very weak effects on norepinephrine and dopamine neuronal reuptake.

12.3 Pharmacokinetics

Absorption

Tablets of PAXIL CR contain a degradable polymeric matrix designed to control the dissolution rate of paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release *in vivo*, an enteric coat delays the start of drug release until tablets of PAXIL CR have left the stomach.

Paroxetine extended-release tablets are completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine C_{max} and $AUC_{0\text{-}inf}$ increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and $AUC_{0\text{-}inf}$ values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL, and 121, 261, 338, and 540 ng•hr. /mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The bioavailability of 25 mg PAXIL CR is not affected by food.

Distribution

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Elimination

Metabolism

The mean elimination half-life of paroxetine was 15 to 20 hours throughout a range of single doses of PAXIL CR (12.5 mg, 25 mg, 37.5 mg, and 50 mg). During repeated administration of PAXIL CR (25 mg once daily), steady state was reached within 2 weeks (i.e., comparable to

immediate-release formulations). In a repeat-dose study in which normal male and female subjects (n = 23) received PAXIL CR (25 mg daily), mean steady state C_{max}, C_{min}, and AUC_{0-24} values were 30 ng/mL, 20 ng/mL, and 550 ng•hr./mL, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on AUC_{0-24} was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway (Figure 3).

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions *[see Drug Interactions (7.3)]*.

Excretion
Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

The elimination half-life is approximately 15 to 20 hours after a single dose of PAXIL CR. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Drug Interaction Studies
There are clinically significant, known drug interactions between paroxetine and other drugs *[see Drug Interactions (7)]*.

Figure 1. Impact of Paroxetine on the Pharmacokinetics of Co-Administered Drugs (log scale)

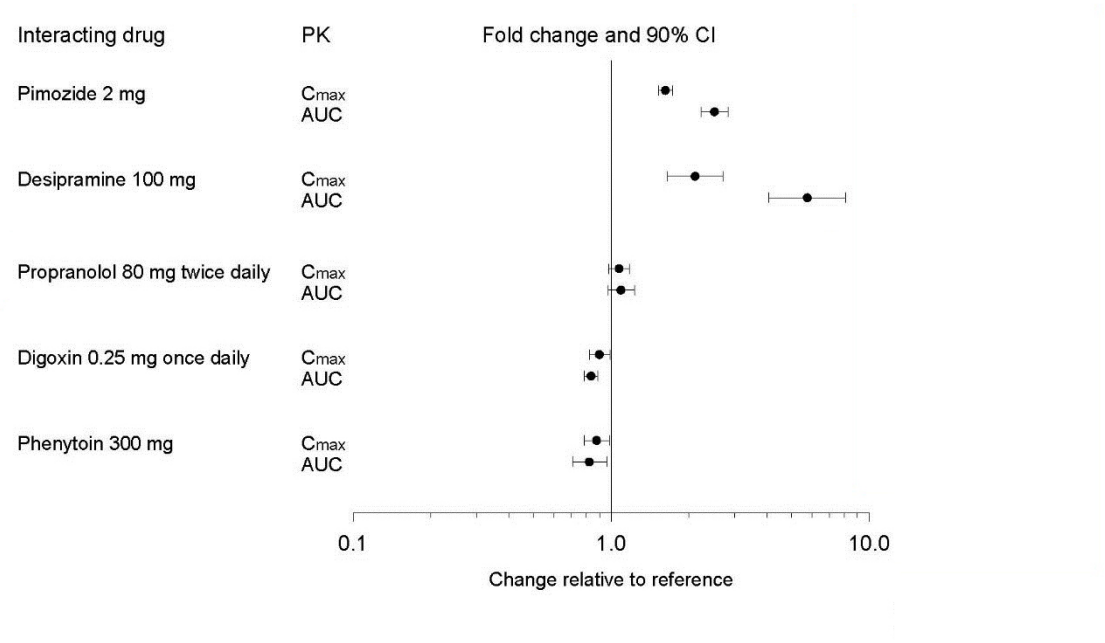
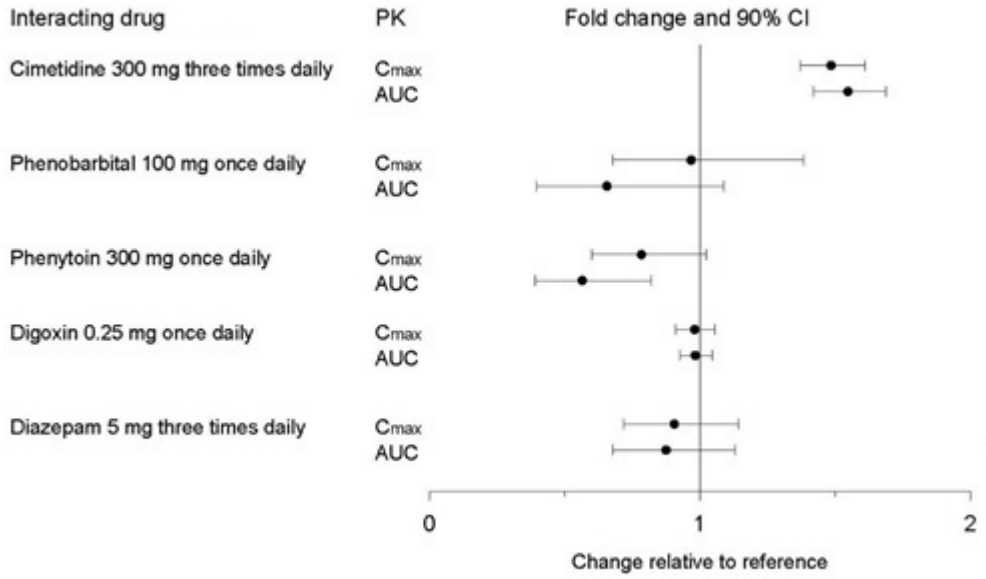


Figure 2. Impact of Co-Administered Drugs on the Pharmacokinetics of Paroxetine

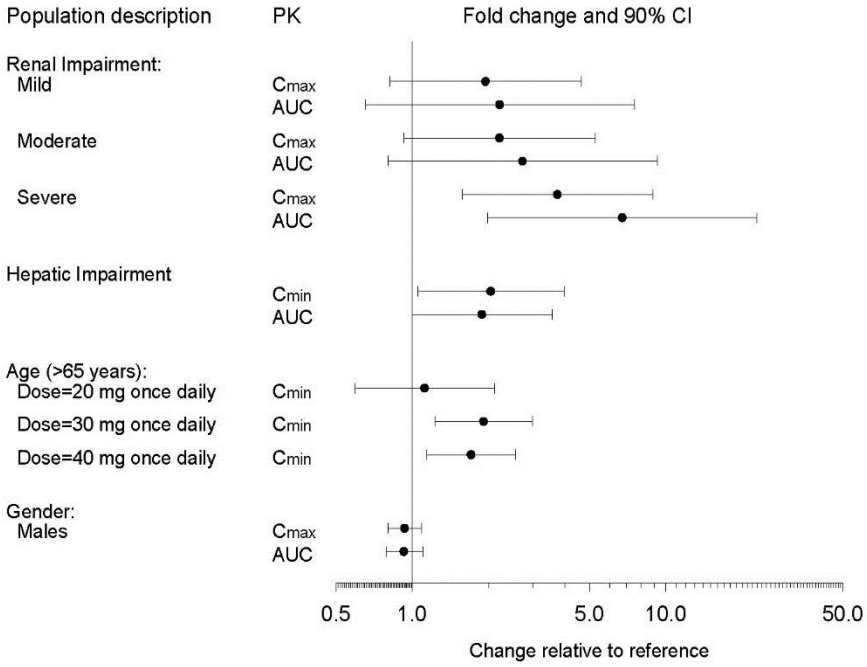


Theophylline: Reports of elevated theophylline levels associated with immediate-release paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Drugs Metabolized by Cytochrome CYP3A4
An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Paroxetine's extent of inhibition of CYP3A4 activity is not expected to be of clinical significance.

Specific Populations
The impact of specific populations on the pharmacokinetics of paroxetine are shown in Figure 3.

Figure 3. Impact of Specific Population on the Pharmacokinetics of Paroxetine (log scale)



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 1.6 (mouse) and 2.5 (rat) times the MRHD on an mg/m^2 basis. There was a significantly greater

number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility

Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality during SSRI treatment, which may affect fertility in some men.

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on an mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 6 and 3 times the MRHD on an mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

The efficacy of PAXIL CR as a treatment for major depressive disorder (MDD) was established in two 12-week, multicenter, randomized, double-blind, placebo-controlled, flexible dose studies with PAXIL CR (Study 1 and Study 2) in adult patients who met Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for MDD. Study 1 and 2 included patients 18 to 65 years old who received PAXIL CR doses of 25 to 62.5 mg/day (N= 212) or placebo (N= 211) once daily compared to immediate-release paroxetine 20 to 50 mg (N=217). A third 12-week, multicenter, randomized, double-blind, placebo-controlled, flexible dose study with PAXIL CR (Study 3) included elderly patients, ranging in age from 60 to 88 years old and used PAXIL CR doses of 12.5 to 50 mg/day (N=104) or placebo (N=109) once daily compared to immediate-release paroxetine 10 to 40 mg (N=106). In all three studies, PAXIL CR was statistically superior to placebo in improving depressive symptoms as measured by the following: the mean change from baseline in the Hamilton Depression Rating Scale (HDRS) total score at Week 12, the mean change from baseline in the Hamilton Depressed Mood item score at Week 12, and the mean change from baseline in the Clinical Global Impression (CGI)–Severity of Illness score.

Long-term efficacy of paroxetine for treatment of MDD in outpatients was established with one randomized withdrawal study with immediate-release paroxetine. Patients who responded to immediate-release paroxetine (HDRS total score <8) during an initial 8-week open-label treatment phase were then randomized to continue immediate-release paroxetine or placebo, for up to 1 year. Patients treated with immediate-release paroxetine demonstrated a statistically

significant lower relapse rate during the withdrawal phase (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

14.2 Panic Disorder

The effectiveness of PAXIL CR in the treatment of panic disorder (PD) was evaluated in three 10-week, multicenter, flexible-dose studies (Studies 4, 5, and 6) comparing PAXIL CR (12.5 to 75 mg daily) to placebo in adult outpatients 19 to 72 years of age who met panic disorder (with or without agoraphobia) criteria according to DSM-IV. These trials were assessed on the basis of their outcomes on 3 variables: (1) the proportions of patients free of full panic attacks at Week 10; (2) change from baseline to Week 10 in the median number of full panic attacks; and (3) change from baseline to Week 10 in the median Clinical Global Impression Severity score. For Studies 4 and 5, PAXIL CR was superior to placebo on 2 of these 3 variables. Study 6 failed to consistently demonstrate a statistically significant difference between PAXIL CR and placebo on any of these variables.

For all 3 studies, the mean dose of PAXIL CR for completers at Week 10 was approximately 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Long-term maintenance effects of paroxetine in patients with PD were demonstrated in a randomized-withdrawal study using immediate-release paroxetine. Patients who were responders during a 10-week, double-blind trial (followed by a 3-month double-blind maintenance phase) of immediate-release paroxetine were re-randomized to continue immediate-release paroxetine or placebo in a 3-month, double-blind withdrawal phase. Patients randomized to immediate-release paroxetine were statistically significantly less likely to relapse than placebo-treated patients.

14.3 Social Anxiety Disorder

The efficacy of PAXIL CR as a treatment for social anxiety disorder (SAD) was established, in part, on the basis of extrapolation from the established effectiveness of immediate-release paroxetine in the treatment of SAD. In addition, the effectiveness of PAXIL CR in the treatment of SAD was demonstrated in one 12-week, multicenter, double-blind, flexible-dose, placebo-controlled study of adult outpatients with a primary diagnosis of SAD by DSM-IV criteria (Study 7). In Study 7, the effectiveness of PAXIL CR (12.5 to 37.5 mg daily) compared to placebo was evaluated on the basis of (1) change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score at Week 12 and (2) the proportion of responders who scored 1 or 2 (very much improved or much improved) on the CGI Global Improvement score at Week 12.

In Study 7, PAXIL CR demonstrated statistically significant superiority over placebo on both the change on LSAS total score at Week 12 and the CGI Improvement responder criterion at Week 12. For patients who completed the trial, 64% of patients treated with PAXIL CR compared to 35% of patients treated with placebo were CGI Improvement responders at Week 12.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of gender. Subgroup analyses of studies utilizing the immediate-release formulation of paroxetine generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

14.4 Premenstrual Dysphoric Disorder

The effectiveness of PAXIL CR for the treatment of Premenstrual Dysphoric Disorder (PMDD) utilizing a continuous dosing regimen has been established in 2 placebo-controlled trials in female patients ages 18 to 46 (Studies 8 and 9 [N=672]). Patients in these trials met DSM-IV criteria for PMDD. Of 1,030 patients including Study 10, who were treated with daily doses of PAXIL CR 12.5 or 25 mg/day, or placebo continuously throughout the menstrual cycle for a period of 3 menstrual cycles, the mean duration of the PMDD symptoms was approximately 11 ± 7 years. Patients on systemic hormonal contraceptives were excluded from these trials. Therefore, the efficacy of PAXIL CR in combination with systemic (including oral) hormonal contraceptives for the continuous daily treatment of PMDD is unknown.

The VAS score is a patient-rated instrument that mirrors the diagnostic criteria of PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms, and other symptoms associated with PMDD. In Studies 8 and 9, 12.5 mg/day and 25 mg/day of PAXIL CR were statistically significantly more effective than placebo as measured by change from baseline to Month 3 on the luteal phase VAS score.

In an additional study employing luteal phase dosing (Study 11), patients (N = 366) were treated for the 2 weeks prior to the onset of menses with 12.5 or 25 mg/day of PAXIL CR or placebo for a period of 3 months. In this trial,12.5 mg/day and 25 mg/day of PAXIL CR, as luteal phase dosing, was statistically significantly more effective than placebo as measured by change from baseline to luteal phase VAS score at Month 3.

There is insufficient information to determine the effect of race or age on outcome in Studies 8, 9, 10, and 11.

16 HOW SUPPLIED/STORAGE AND HANDLING

PAXIL CR is supplied as a round, extended-release tablet as follows:

- 12.5-mg yellow tablets, engraved on one side with “GSK” and engraved on the other side with “12.5”.
  Bottles of 30 with child-resistant closure, NDC 60505-3668-3
- 25-mg pink tablets, engraved on one side with “GSK” and engraved on the other side with “25”.
  Bottles of 30 with child-resistant closure, NDC 60505-3669-3
- 37.5 mg blue tablets, engraved on one side with “GSK” and engraved on the other side with “37.5”.
  Bottles of 30 with child-resistant closure, NDC 60505-3670-3

Store at or below 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down, and instruct them to report such symptoms to the healthcare provider *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Important Administration Instructions

Instruct patients to swallow PAXIL CR whole and to not chew or crush the tablets *[see Dosage and Administration (2.1)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of PAXIL CR with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid). Instruct patients to contact their health care provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome *[see Warnings* and *Precautions (5.2), Drug Interactions (7.1)]*.

Concomitant Medications

Advise patients to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for drug-drug interactions *[see Warning and Precautions (5.3), Drug Interactions (7)]*.

Increased Risk of Bleeding

Inform patients about the concomitant use of PAXIL CR with aspirin, NSAIDs, other antiplatelet drugs, warfarin, or other anticoagulants because the combined use has been associated with an increased risk of bleeding. Advise patients to inform their health care providers if they are taking or planning to take any prescription or over-the counter medications that increase the risk of bleeding *[see Warnings and Precautions (5.5)]*.

Activation of Mania/Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania and instruct them to report such symptoms to the healthcare provider *[see Warnings and Precautions (5.6)]*.

Discontinuation Syndrome

Advise patients not to abruptly discontinue PAXIL CR and to discuss any tapering regimen with their healthcare provider. Inform patients that adverse reactions can occur when PAXIL CR is discontinued *[See Warnings and Precautions (5.7)]*.

Sexual Dysfunction

Advise patients that use of PAXIL CR may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider *[see Warnings* and *Precautions (5.13)]*.

Allergic Reactions

Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing *[see Adverse Reactions (6.1, 6.2)]*.

Embryo-Fetal Toxicity

Advise women of the potential risk to the fetus *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy because of the risk to the fetus.

Nursing

Advise women to notify their healthcare provider if they are breastfeeding an infant *[see Use in Specific Populations (8.3)]*.

Manufactured by: **Apotex Inc.** Toronto, Ontario M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL 33326

Medication Guide
PAXIL CR (PAX-il)
(paroxetine)
extended-release tablets

What is the most important information I should know about PAXIL CR?

PAXIL CR can cause serious side effects, including:

- **Increased risk of suicidal thoughts or actions.** Antidepressant medicines may increase suicidal thoughts and actions in some children and young adults within the first few months of treatment or when the dose is changed. PAXIL CR is not for use in people younger than 18 years of age.

  How can I watch for and try to prevent suicidal thoughts and actions?

  - Depression or other serious mental illnesses are the most important causes of suicidal thoughts and actions.
  - Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts or feelings or if you develop suicidal thoughts or actions. This is very important when an antidepressant medicine is started or when the dose is changed.
  - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts or feelings or if you develop suicidal thoughts or actions.
  - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

  Call your healthcare provider or get emergency medical help right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

  - attempts to commit suicide
  - acting aggressive or violent
  - new or worse depression
  - feeling agitated, restless, angry, or irritable
  - an increase in activity and talking more than what is normal for you
  - acting on dangerous impulses
  - thoughts about suicide or dying
  - new or worse anxiety or panic attacks
  - trouble sleeping
  - other unusual changes in behavior or mood

What is PAXIL CR?

PAXIL CR is a prescription medicine used in adults to treat:

- A certain type of depression called Major Depressive Disorder (MDD)
- Panic Disorder
- Social Anxiety Disorder (SAD)
- Premenstrual Dysphoric Disorder (PMDD)

Do not take PAXIL CR if you:

- take a monoamine oxidase inhibitor (MAOI)
- have stopped taking an MAOI in the last 14 days
- are being treated with the antibiotic linezolid or intravenous methylene blue
- are taking thioridazine
- are taking pimozide
- are allergic to paroxetine or any of the ingredients in PAXIL CR. See the end of this Medication Guide for a complete list of ingredients in PAXIL CR.

Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI or one of these medicines, including intravenous methylene blue.

Do not start taking an MAOI for at least 14 days after you stop treatment with PAXIL CR.

Before taking PAXIL CR, tell your healthcare provider about all your medical conditions, including if you:

- have heart problems
- have or had bleeding problems
- have, or have a family history of bipolar disorder, mania or hypomania
- have or had seizures or convulsions
- have glaucoma (high pressure in the eye)
- have low sodium levels in your blood
- have bone problems

- have kidney or liver problems
- are pregnant or plan to become pregnant. PAXIL CR may harm your unborn baby. Talk to your healthcare provider about the risks to your unborn baby if you take PAXIL CR during pregnancy. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with PAXIL CR.
- are breastfeeding or plan to breastfeed. PAXIL CR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with PAXIL CR.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

PAXIL CR and some other medicines may affect each other causing possible serious side effects. PAXIL CR may affect the way other medicines work and other medicines may affect the way PAXIL CR works.

Especially tell your healthcare provider if you take:

- medicines used to treat migraine headaches called triptans
- tricyclic antidepressants
- fentanyl
- lithium
- tramadol
- tryptophan
- buspirone
- amphetamines
- St. John's Wort
- medicines that can affect blood clotting such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or warfarin
- diuretics
- tamoxifen

Ask your healthcare provider if you are not sure if you are taking any of these medicines. Your healthcare provider can tell you if it is safe to take PAXIL CR with your other medicines.

Do not start or stop any other medicines during treatment with PAXIL CR without talking to your healthcare provider first. Stopping PAXIL CR suddenly may cause you to have serious side effects. See, **"What are the possible side effects of PAXIL CR?"**

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take PAXIL CR?

- Take PAXIL CR exactly as your healthcare provider tell you to. Your healthcare provider may need to change the dose of PAXIL CR until it is the right dose for you.
- Take PAXIL CR 1 time each day in the morning.
- PAXIL CR may be taken with or without food.
- Swallow PAXIL CR tablets whole. **Do not** chew or crush PAXIL CR tablets.
- If you take too much PAXIL CR, call your poison control center at 1-800-222-1222 or got to the nearest hospital emergency room right away.

What are possible side effects of PAXIL CR?

PAXIL CR can cause serious side effects, including:

- See, **"What is the most important information I should know about PAXIL CR?"**
- **Serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when you take PAXIL CR with certain other medicines. See, "Who should not take PAXIL CR?" **Call your healthcare provider or go to the nearest hospital emergency room right away** if you have any of the following signs and symptoms of serotonin syndrome:
  - agitation
  - seeing or hearing things that are not real (hallucinations)
  - confusion
  - coma
  - fast heart beat
  - changes in blood pressure
  - dizziness
  - sweating
  - flushing
  - high body temperature (hyperthermia)
  - shaking (tremors), stiff muscles, or muscle twitching
  - loss of coordination
  - seizures
  - nausea, vomiting, diarrhea

- **Medicine interactions.** Taking PAXIL CR with certain other medicines including thioridazine and pimozide may increase the risk of developing a serious heart problem called QT prolongation.
- **Abnormal bleeding.** Taking PAXIL CR with aspirin, NSAIDs, or blood thinners may add to this risk. Tell your healthcare provider about any unusual bleeding or bruising.
- **Manic episodes.** Manic episodes may happen in people with bipolar disorder who take PAXIL CR. Symptoms may include:
  - greatly increased energy
  - racing thoughts
  - unusually grand ideas
  - talking more or faster than usual
  - severe problems sleeping
  - reckless behavior
  - excessive happiness or irritability
- **Discontinuation syndrome.** Suddenly stopping PAXIL CR may cause you to have serious side effects. Your healthcare provider may want to decrease your dose slowly. Symptoms may include:
  - nausea
  - sweating
  - changes in your mood
  - irritability and agitation
  - dizziness
  - electric shock feeling (paresthesia)
  - tremor
  - anxiety
  - confusion
  - headache
  - tiredness
  - problems sleeping
  - ringing in your ears (tinnitus)
  - seizures
- **Seizures (convulsions).**

  Eye problems (angle-closure glaucoma). PAXIL CR may cause a type of eye problem called angle-closure glaucoma in people with certain other eye conditions. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.
- **Low sodium levels in your blood (hyponatremia).** Low sodium levels in your blood that may be serious and may cause death, can happen during treatment with PAXIL CR. Elderly people and people who take certain medicines may be at a greater risk for developing low sodium levels in your blood. Signs and symptoms may include:
  - headache
  - difficulty concentrating
  - memory changes
  - confusion
  - weakness and unsteadiness on your feet which can lead to falls

  In more severe or more sudden cases, signs and symptoms include:
  - seeing or hearing things that are not real (hallucinations)
  - fainting
  - seizures
  - coma
  - stopping breathing (respiratory arrest)
- **Bone fractures.**
- **Sexual problems (dysfunction).** Taking selective serotonin reuptake inhibitors (SSRIs), including PAXIL CR, may cause sexual problems.

  Symptoms in males may include:
  - Delayed ejaculation or inability to have an ejaculation
  - Decreased sex drive
  - Problems getting or keeping an erection

  Symptoms in females may include:
  - Decreased sex drive
  - Delayed orgasm or inability to have an orgasm

Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with PAXIL CR. There may be treatments your healthcare provider can suggest.

The most common side effects PAXIL CR include:

- male and female sexual function problems
- blurred vision
- weakness (asthenia)
- dry mouth
- problems sleeping
- nausea

- constipation
- decreased appetite
- diarrhea
- dizziness
- sleepiness
- sweating
- tremor

These are not all the possible side effects of PAXIL CR.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PAXIL CR?

- Store PAXIL CR at room temperature between 68°F to 77°F (20°C to 25°C).

Keep PAXIL CR and all medicines out of the reach of children.

General information about the safe and effective use of PAXIL CR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take PAXIL CR for a condition for which it was not prescribed. Do not give PAXIL CR to other people, even if they have the same symptoms that you have. It may harm them. You may ask your healthcare provider or pharmacist for information about PAXIL CR that is written for healthcare professionals.

What are the ingredients in PAXIL CR?

Active ingredient: paroxetine hydrochloride

Inactive ingredients: glyceryl behenate, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer type C, polyethylene glycols, polysorbate 80, polyvinylpyrrolidone, silicon dioxide, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate and the following colorants: D&C Red No. 30 aluminum lake (25 mg), D&C Yellow No. 10 aluminum lake (12.5 mg), FD&C Blue No. 2 aluminum lake (37.5 mg), FD&C Yellow No. 6 aluminum lake (12.5 mg), red ferric oxide (25 mg) and Yellow ferric oxide (12.5 mg and 37.5 mg).

Manufactured by:

Apotex Inc. Toronto, Ontario M9L 1T9

Manufactured for:
Apotex Corp. Weston, FL 33326

For more information about PAXIL CR call 1-800-706-5575.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 9/2021