

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

- Prior to initiating treatment with PAXIL, screen patients for a personal or family history of bipolar disorder, mania, or hypomania (2.1, 5.6)
- Administer PAXIL as a once daily dose in the morning, with or without food. Administer the tablets or the oral suspension. Shake oral suspension well before administration (2.2)
- Recommended starting and maximum daily dosage for MDD, OCD, PD, and PTSD in the table below. If inadequate response to starting dosage, increase the dosage by 10 mg/day at weekly intervals (e.g., if the starting dosage is 20 mg/day increase the dosage the next week to 30 mg/day) to the maximum dosage: (3)

Indication	Starting Daily Dosage	Maximum Daily Dosage
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 is 20 mg once daily. After 1-2 weeks, may increase the PAXIL dosage by 10 mg/day in weekly intervals (e.g., after 1-2 weeks may increase the PAXIL dosage from 20 mg/day to 30 mg/day) up to a maximum dosage of 60 mg once daily (2.4)
- Recommended starting dosage for GAD is 10 mg once daily. After one week, increase the dosage to 20 mg once daily. In patients with an inadequate response, may increase the PAXIL dosage by 10 mg/day at weekly intervals (e.g., after 1 week may increase the PAXIL dosage from 20 mg/day to 30 mg/day), up to a maximum of 50 mg/day (2.5)
- Geriatric patients, patients with severe renal impairment or severe hepatic impairment: Starting dosage is 10 mg daily and the maximum dosage is 40 mg daily. (2.4)
- When discontinuing PAXIL, reduce dosage gradually. (2.6, 5.7)

DOSAGE FORMS AND STRENGTHS

- Tablets: 10 mg, 20 mg, 30 mg, and 40 mg. (3)
- Oral suspension: 10 mg/5 mL (not currently marketed) (3)

CONTRAINDICATIONS

PAXIL is contraindicated in patients:

- Taking, or within 14 days of stopping monoamine oxidase inhibitors (MAOIs) (4, 5.2, 7)
- Who receive drugs that can prolong QTc interval and are also CYP2D6 substrates (4, 5.3, 7)
- Known hypersensitivity to paroxetine or to any of the inactive ingredients in PAXIL. (4)

WARNINGS and PRECAUTIONS

- **Serotonin Syndrome:** Monitor all patients taking PAXIL for the emergence of serotonin syndrome. If occurs, immediately discontinue PAXIL and serotonergic agents and initiate supportive measures. (5.2)
- **Embryofetal Toxicity:** For women who intend to become pregnant or who are in their first trimester of pregnancy, PAXIL, should be initiated only after consideration of the other available treatment options (5.4, 8.1)
- **Increased Risk of Bleeding:** For patients taking warfarin, carefully monitor the international normalized ratio when initiating, titrating, or discontinuing PAXIL (5.5)
- **Seizures:** Use with caution in patients with seizure disorders. Discontinue PAXIL in any patient who develop a seizure (5.8)
- **Angle-Closure Glaucoma:** Avoid use of PAXIL in patients with untreated anatomically narrow angles. (5.9)
- **Hyponatremia:** In patients with symptomatic hyponatremia, discontinue PAXIL and institute appropriate medical intervention (5.10)
- **Sexual Dysfunction:** Inquire about sexual function prior to initiation of PAXIL and to inquire specifically about changes in sexual function during PAXIL treatment (5.11)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$ 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)
- **CYP2D6 Substrates:** Reduce dosage of the CYP2D6 substrate if needed. (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:** Advise women of the risks associated with first trimester use of PAXIL, risks associated with third trimester use of PAXIL including an increased risk for neonatal complications including persistent pulmonary hypertension of the newborn. Also, advise women of the risks associated with untreated depression in pregnancy in those being treated for MDD (8.1).(8.1)
- **Lactation:** Infants exposed to paroxetine through breastfeeding should be monitored for agitation, irritability, poor feeding and poor weight gain (8.2)
- **Males of Reproductive Potential:** Paroxetine may affect sperm quality which may impair fertility; it is not known if this effect is reversible (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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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 for the treatment of:

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

2 DOSAGE AND ADMINISTRATION

2.1 Screen for Bipolar Disorder Prior to Starting PAXIL

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

2.2 Important Administration Instructions

Administer PAXIL as a once daily dose in the morning, with or without food [see Clinical Pharmacology (12.3)]. Administer the tablets or the oral suspension.

Shake the oral suspension well before administration.

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

The recommended starting dosages and maximum dosages of PAXIL in patients with major depressive disorder (MDD), obsessive compulsive disorder (OCD), panic disorder (PD), and posttraumatic stress disorder (PTSD) are presented in Table 1. In patients with an inadequate response, increase PAXIL dosage by 10 mg/day at weekly intervals (e.g., if the starting dosage is 20 mg/day increase the dosage the next week to 30 mg/day), depending on tolerability, up to the maximum recommended dosage.

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

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

2.4 Recommended Dosage for SAD

The recommended starting dosage of PAXIL in adult patients with social anxiety disorder (SAD) is 20 mg once daily. After 1-2 weeks, may increase the PAXIL dosage by 10 mg/day in weekly intervals (e.g., after 1-2 weeks may increase the PAXIL dosage from 20 mg/day to 30 mg/day) up to a maximum dosage of 60 mg once daily.

In clinical trials the effectiveness of PAXIL for the treatment of SAD was demonstrated in adult patients dosed in a range of 20 mg once daily to 60 mg once daily (after dosage titration). Available information does not suggest any additional benefit for a PAXIL dosage above 20 mg once daily for the treatment of SAD [*see Clinical Studies (14.4)*].

2.5 Recommended Dosage for GAD

The recommended starting PAXIL dosage in adult patients with generalized anxiety disorder (GAD) is 10 mg once daily. After one week, increase the PAXIL dosage to 20 mg once daily. In patients with an inadequate response, may increase the PAXIL dosage by 10 mg/day at weekly intervals (e.g., after 1 week may increase the PAXIL dosage from 20 mg/day to 30 mg/day), depending on tolerability, up to a maximum of 50 mg/day.

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

2.6 Recommended Dosage in Geriatric Patients, Patients with Severe Renal Impairment, and Patients with Severe Hepatic Impairment

The recommended starting PAXIL dosage is 10 mg/day in geriatric patients, patients with severe renal impairment, and patients with severe hepatic impairment. The maximum recommended dosage in these patients is 40 mg/day.

2.7 Switching Patients to or From a Monoamine Oxidase Inhibitor

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)*].

2.8 Discontinuation of PAXIL Treatment

When discontinuing PAXIL treatment, gradually reduce the dosage rather than stopping PAXIL abruptly whenever possible [*see Warnings and Precautions (5.7) and Drug Abuse and Dependence (9.3)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 10 mg yellow, functionally scored engraved on the front with “PAXIL” and on the back with “10”.

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

Oral suspension:

- 10 mg/5 mL orange colored, orange flavored suspension in bottles containing 250 mL (not currently marketed).

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) and Drug Interactions (7)*].
- Who receive drugs that can prolong QTc interval and are also CYP450 2D6 substrates [*see Drug Interactions (7) and Warnings and Precautions (5.3)*]
- With known hypersensitivity to paroxetine or any of the inactive ingredients in PAXIL. Hypersensitivity reactions have included anaphylaxis, angioedema, and Stevens-Johnson syndrome [*see Adverse Reactions (6.1), (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Pediatric Patients 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 were differences in absolute risk of suicidal thoughts and behaviors across the different uses, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 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 Pediatric¹ 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

¹ PAXIL is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in pediatric patients 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.

Closely monitor all antidepressant-treated patients 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

Selective serotonin reuptake inhibitors (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, meperidine, methadone, 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 PAXIL is 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 of administration (such as orally 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) and Drug Interactions (7)*].

Monitor all patients taking PAXIL for the emergence of serotonin syndrome. Discontinue treatment with PAXIL and any concomitant serotonergic drug 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 QTc Interval Prolongation

Cases of QTc interval prolongation have been reported with the use of paroxetine, although causal relationship with PAXIL has not been established.

PAXIL is a strong CYP2D6 inhibitor. Concomitant use of PAXIL with CYP2D6 substrates that prolong the QTc interval can increase the concentration of those CYP2D6 substrates and may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de pointes, other serious arrhythmias, and sudden death.

The concomitant use of PAXIL is contraindicated with CYP2D6 substrates that prolong the QTc interval [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

5.4 Embryofetal Toxicity

PAXIL can cause fetal harm when administered to a pregnant woman. Based on meta-analyses of epidemiological studies, exposure to paroxetine in the first trimester of pregnancy is associated with a less than 2-fold increase in the rate of cardiovascular malformations among infants.

For women who intend to become pregnant or who are in their first trimester of pregnancy, PAXIL, should be initiated only after consideration of the other available treatment options [*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. Based on data from the published observational studies, exposure to SSRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage [*see Use in Specific Populations (8.1)*]. 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 when initiating, titrating, or discontinuing PAXIL.

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 for unipolar depression, hypomania or mania occurred in approximately 1% of PAXIL-treated patients compared to 1.1% of active-control and 0.3% of placebo-treated 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.

During clinical trials of GAD and PTSD, gradual decreases in the daily PAXIL dosage 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 *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.4)*].

When discontinuing PAXIL, a gradual reduction in dosage rather than abrupt cessation is recommended whenever possible [see *Dosage and Administration (2.7)*].

5.8 Seizures

PAXIL has 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 a seizure.

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 hyponatremia 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).

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)*].

In patients with symptomatic hyponatremia, discontinue PAXIL and institute appropriate medical intervention.

5.11 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.

Recommend prescribers inquire about sexual function prior to initiation of PAXIL and to inquire specifically about changes in sexual function during PAXIL treatment because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtain a detailed history (including timing of symptom onset) 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 for sexual dysfunction.

5.12 Risk of Reduced of Efficacy of Tamoxifen

Some studies have shown that the efficacy of tamoxifen, as measured by breast cancer relapse and mortality, may be reduced with concomitant use of PAXIL as a result of paroxetine's irreversible CYP2D6 inhibition and lower concentration of the active metabolite of tamoxifen [see *Drug Interactions* (7)]. One study suggested that the risk may increase with longer duration of concomitant use of PAXIL and tamoxifen. 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 rather than PAXIL.

5.13 Fracture Risk

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

6 ADVERSE REACTIONS

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

- Suicidal thoughts and behaviors [see *Warnings and Precautions* (5.1)]
- Serotonin syndrome [see *Warnings and Precautions* (5.2)]
- 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)]
- Sexual Dysfunction [see *Warnings and Precautions* (5.11)]
- Fracture [see *Warnings and Precautions* (5.12)]

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 six-week clinical trials in adult patients with MDD. Patients in the PAXIL group received PAXIL 20 mg to 50 mg once daily (Studies MDD-1, MDD-2, MDD-3, MDD-4, MDD-5, and MDD-6) [see *Clinical Studies (14.1)*].
- 2 twelve-week clinical trials in adult patients with OCD. Patients in the PAXIL group received PAXIL 20 mg to 60 mg once daily (Studies OCD-1 and OCD-2) [see *Clinical Studies (14.2)*].
- 3 ten to twelve-week clinical trials in adult patients with PD. Patients in the PAXIL group received PAXIL 10 mg to 60 mg once daily (Studies PD-1, PD-2, and PD-3) [see *Clinical Studies (14.3)*].
- 3 twelve-week clinical trials in adult patients with SAD. Patients in the PAXIL group received PAXIL 20 mg to 50 mg once daily (Studies SAD-1, SAD-2, and SAD-3) [see *Clinical Studies (14.4)*].
- 3 eight-week clinical trials in adult patients with GAD. Patients in the PAXIL group received PAXIL 10 mg to 50 mg once daily (Studies GAD-1, GAD-2, and GAD-3) [see *Clinical Studies (14.5)*].
- 2 twelve-week clinical trials in adult patients with PTSD. Patients in the PAXIL group received PAXIL 20 mg to 50 mg once daily (Studies PTSD -1 and PTSD -2) [see *Clinical Studies (14.6)*].

Adverse Reactions Leading to Discontinuation

In clinical studies in adults with MDD, SAD, OCD, PD, GAD, and PTSD, 20% (1,199/6,145), 16% (84/522), 12% (64/542), 9% (44/469), 11% (79/735), and 12% (79/676) of PAXIL-treated patients, 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 the PAXIL group compared to the placebo group) are presented in Table 3.

Table 3: Adverse Reactions That Led to Discontinuation (≥1% of PAXIL-Treated Patients and Greater than Placebo) in MDD, OCD, PD, SAD, GAD, and PTSD Adult Studies

	MDD		OCD		PD		SAD		GAD		PTSD	
	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo
CNS Adverse Reactions												
Somnolence	2.3%	0.7%	—	—	1.9%	0.3%	3.4%	0.3%	2%	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%	0.2%
Anxiety	—	—	—	—	—	—	1.1%	0%	—	—	—	—
Dizziness	—	—	1.5%	0%	—	—	1.9%	0%	1%	0.2%	—	—
Gastrointestinal Adverse Reactions												
Constipation	—	—	1.1%	0%	—	—	—	—	—	—	—	—
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%	4%	0.3%	2%	0.2%	2.2%	0.6%
Diarrhea	1%	0.3%	—	—	—	—	—	—	—	—	—	—
Dry mouth	1%	0.3%	—	—	—	—	—	—	—	—	—	—
Vomiting	1%	0.3%	—	—	—	—	1%	0%	—	—	—	—
Flatulence	—	—	—	—	—	—	1%	0.3%	—	—	—	—
Other Adverse Reactions												
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%	0.3%	—	—	—	—	1.1%	0%	1.1%	0.2%	—	—
Impotence ^a	—	—	1.5%	0%	—	—	—	—	—	—	—	—
Libido Decreased	—	—	—	—	—	—	1%	0%	—	—	—	—

If numbers are not provided in the table, the incidence of the adverse reactions in PAXIL-treated patients was not >1% or was not ≥ 2 times the incidence in placebo-treated patients .

^a. Incidence corrected for sex.

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 Adult Patients with MDD

Table 4 presents the adverse reactions that occurred at an incidence of 1% or more and greater in the PAXIL group than the placebo group in clinical trials in adult patients with MDD (Studies MDD-1, MDD-2, MDD-3, MDD-4, MDD-5, and MDD-6).

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

	PAXIL (n = 421)	Placebo (n = 421)
Nausea	26%	9%
Somnolence	23%	9%
Dry Mouth	18%	12%
Headache	18%	17%
Asthenia	15%	6%
Constipation	14%	9%
Ejaculatory Disturbance ^a	13%	0%
Dizziness	13%	6%
Insomnia	13%	6%
Diarrhea	12%	8%
Sweating	11%	2%
Other Male Genital Disorders ^b	10%	0%
Tremor	8%	2%
Decreased Appetite	6%	2%
Nervousness	5%	3%
Anxiety	5%	3%
Yawn	4%	0%
Blurred Vision	4%	1%
Flatulence	4%	2%
Paresthesia	4%	2%
Palpitation	3%	1%
Vasodilation	3%	1%
Libido Decreased	3%	0%
Urination Disorder ^d	3%	0%
Urinary Frequency	3%	1%
Taste Perversion	2%	0%
Female Genital Disorders ^d	2%	0%
Oropharynx Disorder ^c	2%	0%
Myopathy	2%	1%
Dyspepsia	2%	1%
Rash	2%	1%
Drugged Feeling	2%	1%
Myalgia	2%	1%
Confusion	1%	0%
Myasthenia	1%	0%

a. Ejaculatory disturbance mostly “ejaculatory delay.”

b. Other male genital disorders percentage corrected for sex. Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual dysfunction,” and “impotence.”

c. Urination Disorder Includes mostly “difficulty with micturition” and “urinary hesitancy.”

d. Female Genital Disorders includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”

e. Oropharynx disorder includes mostly “lump in throat” and “tightness in throat.”

Dose dependent adverse reactions in fixed-dose studies (Study MDD-1, MDD-2, MDD-3, MDD-4, MDD-5, and MDD-6) for the treatment of adults with MDD that compared PAXIL 10 mg, 20 mg, 30 mg, and 40 mg once daily with placebo once daily are shown in Table 5.

Table 5. Adverse Reactions ($\geq 5\%$ of PAXIL-Treated Patients and $\geq$ Twice the Rate of Placebo-Treated Patients) in a Study of Adults with MDD (Study MDD-1, MDD-2, MDD-3, MDD-4, MDD-5, and MDD-6)

	Placebo (n = 51)	PAXIL			
		10 mg/day (n=102)	20 mg/day (n=104)	30 mg/day (n=101)	40 mg/day (n=102)
Nausea	14%	15%	27%	35%	36%
Somnolence	8%	13%	18%	21%	22%
Dry Mouth	2%	11%	18%	16%	21%
Diarrhea	8%	10%	19%	8%	15%
Tremor	0%	0%	8%	8%	15%
Asthenia	0%	3%	11%	14%	13%
Abnormal Ejaculation	0%	6%	7%	11%	13%
Constipation	6%	5%	8%	10%	13%
Dizziness	4%	7%	8%	9%	13%
Sweating	2%	1%	7%	9%	12%
Blurred Vision	2%	3%	3%	2%	8%
Anxiety	0%	2%	6%	6%	6%
Paresthesia	0%	3%	1%	5%	6%
Decreased Appetite	2%	2%	6%	4%	5%
Male Genital Disorders	0%	4%	9%	6%	4%
Nervousness	0%	6%	6%	4%	3%
Impotence	0%	2%	4%	6%	2%

Adverse Reactions in Adult Patients with OCD, PD, and SAD

Table 6 presents adverse reactions that occurred at a frequency of 2% or more in clinical trials in adult patients with OCD, PD, and SAD (i.e., Studies OCD-1, OCD-2, PD-1, PD-2, PD-3, SAD-1, SAD-2, and SAD-3).

Dose-related adverse reactions in a 10-week fixed-dose study (Study PD-1) that compared placebo and PAXIL 10 mg, 20 mg, and 40 mg once daily in the treatment of adults with PD were asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation.

There was no clear relationship between adverse reactions and the PAXIL dosage in a:

- Fixed dose study (Study OCD-1) that compared placebo and PAXIL 20 mg, 40 mg, and 60 mg once daily in the treatment of adults with OCD.
- Fixed dose study (SAD-3) that compared placebo and PAXIL 20 mg, 40 mg and 60 mg once daily in the treatment of adults with SAD.

Table 6. Adverse Reactions ($\geq 2\%$ of PAXIL-Treated Patients and Greater than Placebo-Treated Patients) in 10 to 12-Week Clinical Trials for OCD, PD, and SAD

	OCD		PD		SAD	
	PAXIL (n = 542)	Placebo (n = 265)	PAXIL (n = 469)	Placebo (n = 324)	PAXIL (n = 425)	Placebo (n = 339)
Somnolence	24%	7%	19%	11%	22%	5%
Insomnia	24%	13%	18%	10%	21%	16%
Abnormal Ejaculation ^a	23%	1%	21%	1%	28%	1%
Nausea	23%	10%	23%	17%	25%	7%
Asthenia	22%	14%	14%	5%	22%	14%
Dry Mouth	18%	9%	18%	11%	9%	3%
Constipation	16%	6%	8%	5%	5%	2%
Dizziness	12%	6%	14%	10%	11%	7%
Tremor	11%	1%	9%	1%	9%	1%
Diarrhea	10%	10%	12%	7%	9%	6%
Sweating	9%	3%	14%	6%	9%	2%
Decreased Appetite	9%	3%	7%	3%	8%	2%
Nervousness	9%	8%	—	—	8%	7%
Impotence ^a	8%	1%	5%	0%	5%	1%
Decreased libido	7%	4%	9%	1%	12%	1%
Abnormal Dreams	4%	1%	—	—	—	—
Vasodilation	4%	1%	—	—	—	—
Abnormal Vision	4%	2%	—	—	4%	1%
Increased Appetite	4%	3%	2%	1%	2%	-
Female Genital Disorder ^a	3%	0%	9%	1%	9%	1%
Myoclonus	3%	0%	3%	2%	2%	1%
Depersonalization	3%	0%	—	—	—	—
Urination Impaired	3%	0%	—	—	—	—
Concentration Impaired	3%	2%	—	—	4%	1%
Chest Pain	3%	2%	-	-	-	-
Rash	3%	2%	—	—	—	—
Urinary Frequency	3%	1%	2%	0%	—	—
Palpitation	2%	0%	—	—	—	—
Taste Perversion	2%	0%	—	—	—	—
Chills	2%	1%	2%	1%	—	—
Urinary Tract Infection	2%	1%	2%	1%	—	—
Amnesia	2%	1%	-	-	-	-
Back Pain	-	-	3%	2%	-	-
Agitation	—	—	5%	4%	3%	1%
Anxiety	—	—	5%	4%	5%	4%
Abdominal Pain	-	-	4%	3%	—	—
Rhinitis	-	-	3%	0%	-	-
Yawn	-	-	-	-	5%	1%
Dysmenorrhea	—	—	—	—	5%	4%
Dyspepsia	-	-	-	-	4%	2%
Pharyngitis	—	—	—	—	4%	2%
Myalgia	—	—	—	—	4%	3%
Trauma	—	—	—	—	3%	1%
Flatulence	-	-	-	-	-	2%
Vomiting	-	-	-	-	-	1%

a. Percentage corrected for sex.

Adverse Reactions in Adult Patients with GAD and PTSD

Table 7 presents adverse reactions that occurred at a frequency of 2% or more in clinical trials in adult patients with GAD and PTSD (i.e., Studies GAD-1, GAD-2, PTSD-1, and PTSD-2).

Dose-related adverse reactions in a fixed dose studies that compared:

- Placebo and PAXIL 20 mg and 40 mg once daily in the treatment of adults with GAD were asthenia, constipation, and abnormal ejaculation.
- Placebo and PAXIL 20 mg and 40 mg once daily in the treatment of adults with PTSD were impotence and abnormal ejaculation.

Table 7. Adverse Reactions ($\geq 2\%$ of PAXIL-Treated Patients and Greater than Placebo) in 8- to 12-Week Clinical Trials for GAD and PTSD^a

	Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
	Paxil (n= 735)	Placebo (n = 529)	PAXIL (n = 676)	Placebo (n = 504)
Abnormal Ejaculation ^a	25%	2%	13%	2%
Nausea	20%	5%	19%	8%
Headache	17%	14%	---	---
Somnolence	15%	5%	16%	5%
Asthenia	14%	6%	12%	4%
Dry Mouth	11%	5%	10%	5%
Insomnia	9%	2%	5%	2%
Constipation	10%	2%	5%	3%
Libido Decreased	9%	2%	5%	2%
Diarrhea	9%	7%	11%	5%
Respiratory Disorder	7%	5%	---	---
Sweating	6%	2%	5%	1%
Infection	6%	3%	5%	4%
Dizziness	6%	5%	6%	5%
Decreased Appetite	5%	1%	6%	3%
Tremor	5%	1%	4%	1%
Female Genital Disorder ^a	4%	1%	5%	1%
Yawn	4%	---	2%	<1%
Nervousness	4%	3%	---	---
Sinusitis	4%	3%	---	---
Impotence ^a	4%	3%	9%	1%
Vasodilation	3%	1%	2%	1%
Vomiting	3%	2%	3%	2%
Abnormal Vision	2%	1%	3%	1%
Trauma			6%	5%
Dyspepsia	---	---	5%	3%
Abdominal Pain			4%	3%
Abnormal Dreams			3%	

Male and Female Sexual Dysfunction

The percentage of patients who reported symptoms of sexual dysfunction in males and females with MDD, OCD, PD, SAD, GAD, and PTSD (i.e., Studies MDD-1, MDD-2, MDD-3, MDD-4, MDD-5, and MDD-6; OCD-1 and OCD-2; PD-1, PD-2, and PD-3; SAD-1, SAD-2, and SAD-3; GAD-1 and GAD-2; PTSD-1 and PTSD-2) are displayed in Table 8. 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.

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

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

Males		
	PAXIL (n=1446)	Placebo (n=1042)
Decreased Libido	6% to 15%	0% to 5%
Ejaculatory Disturbance	13% to 28%	0% to 2%
Impotence	2 %to 9%	0% to 3%
Females		
	PAXIL (n=1,822)	Placebo (n=1,340)
Decreased Libido	0% to 9%	0% to 2%
Orgasmic Disturbance	2% to 9%	0% to 1%

Hallucinations

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

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 that occurred on 1 or more occasion in at least 1/100 patients.
- Infrequent adverse reactions are those that occurred in 1/100 to 1/1,000 patients.
- Rare adverse reactions are those that occurred 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 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.

- *Blood system disorders:* events related to impaired hematopoiesis (including agranulocytosis, aplastic anemia, bone marrow aplasia and pancytopenia), hemolytic anemia
- *Cardiac disorders:* torsade de pointes, ventricular fibrillation, ventricular tachycardia
- *Endocrine disorders:* hyperprolactinemia, syndrome of inappropriate antidiuretic hormone (SIADH) secretion
- *Gastrointestinal disorders:* acute pancreatitis
- *Hepatobiliary disorders:* elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction)
- *Immune system disorders:* anaphylactic reaction, vasculitis syndromes (such as Henoch-Schönlein purpura).
- *Metabolism and nutrition disorders:* porphyria
- *Musculoskeletal and connective tissue disorders:* Hypertonia

- *Nervous system disorders:* extrapyramidal symptoms (i.e. akathisia, bradykinesia, cogwheel rigidity, oculogyric crisis which has been associated with concomitant use of pimozide), Guillain-Barré Syndrome, anosmia, hyposmia, optic neuritis, restless legs syndrome (RLS), status epilepticus
- *Pregnancy, puerperium and perinatal conditions:* eclampsia, premature birth
- *Renal disorders:* acute renal failure
- *Reproductive system and breast disorders:* galactorrhea, priapism
- *Respiratory disorders:* allergic alveolitis, laryngospasm, pulmonary hypertension
- *Skin and subcutaneous tissue disorders:* Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)
- *Vascular disorders:* severe hypotension

7 DRUG INTERACTIONS

Table 9 presents clinically significant drug interactions with PAXIL.

Table 9: Clinically Significant Drug Interactions with PAXIL

Monoamine Oxidase Inhibitors	
<i>Mechanism and Clinical Effect(s)</i>	The concomitant use of SSRIs, including PAXIL and monoamine oxidase inhibitors (MAOIs) increases the risk of serotonin syndrome.
<i>Prevention or Management</i>	PAXIL is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue [see <i>Dosage and Administration (2.5)</i> and <i>Warnings and Precautions (5.2)</i>].
CYP2D6 Substrates that Prolong the QTc Interval	
<i>Mechanism and Clinical Effect(s)</i>	PAXIL is a strong CYP2D6 inhibitor. Concomitant use of PAXIL with CYP2D6 substrates that prolong the QTc interval can increase the concentration of those CYP2D6 substrates and may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation [see <i>Warnings and Precautions (5.3)</i>].
<i>Prevention or Management</i>	PAXIL is contraindicated in patients taking drugs that can prolong QTc interval and are CYP2D6 substrates. [see <i>Contraindications (4)</i>].
Other Serotonergic Drugs	
<i>Mechanism and Clinical Effect(s)</i>	The concomitant use of PAXIL with serotonergic drugs increases the risk of serotonin syndrome.
<i>Prevention or Management</i>	Monitor patients for signs and symptoms of serotonin syndrome with concomitant use of PAXIL and other serotonergic drugs. If serotonin syndrome occurs, immediately discontinue treatment with PAXIL and/or concomitant serotonergic drugs [see <i>Warnings and Precautions (5.2)</i>].
Drugs that Interfere with Hemostasis (antiplatelet drugs and anticoagulants)	

<i>Mechanism and Clinical</i>	The concomitant use of an antiplatelet drug or anticoagulant with PAXIL may potentiate the risk of bleeding.
<i>Prevention or Management</i>	Inform patients of the increased risk of bleeding associated with the concomitant use of PAXIL and antiplatelet drugs or anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio when initiating, titrating, or discontinuing PAXIL [see <i>Warnings and Precautions (5.5)</i>].
Drugs Highly Bound to Plasma Protein	
<i>Mechanism and Clinical Effect(s)</i>	Paroxetine 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 paroxetine or other tightly-bound drugs in plasma.
<i>Prevention or Management</i>	Monitor for adverse reactions and reduce dosage of PAXIL or other protein-bound drugs as warranted.
CYP2D6 Substrates	
<i>Mechanism and Clinical Effect(s)</i>	PAXIL is a strong CYP2D6 inhibitor [see <i>Clinical Pharmacology (12.3)</i>]. The concomitant use of PAXIL with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate and increase the risk of CYP2D6 substrate-associated adverse reactions.
<i>Prevention or Management</i>	With concomitant use with PAXIL, decrease the dosage of a CYP2D6 substrate if needed.
Tamoxifen	
<i>Mechanism and Clinical Effect(s)</i>	Concomitant use of tamoxifen with PAXIL may lead to reduced plasma concentrations of the active metabolite of tamoxifen (i.e., endoxifen) and reduced efficacy of tamoxifen
<i>Prevention or Management</i>	Consider use of an alternative antidepressant with little or no CYP2D6 inhibition [see <i>Warnings and Precautions (5.11)</i>].
Fosamprenavir/Ritonavir	
<i>Mechanism and Clinical</i>	Concomitant use of fosamprenavir/ritonavir with PAXIL significantly decreased plasma levels of paroxetine.
<i>Prevention or Management</i>	Any PAXIL dosage modification should be guided by clinical effect (tolerability and efficacy).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or visiting online at <https://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/antidepressants/>.

Risk Summary

For women who intend to become pregnant or who are in their first trimester of pregnancy, PAXIL should be initiated only after consideration of the other available treatment options.

- There are risks of persistent pulmonary hypertension of the newborn (PPHN) (*see Data*) and/or poor neonatal adaptation with exposure to SSRIs including PAXIL during pregnancy (*see Clinical Considerations*).
- Based on data from published observational studies, exposure to SSRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage [*see Warnings and Precautions (5.5) and Clinical Considerations*].
- PAXIL is associated with a less than 2-fold increase in cardiovascular malformations when administered to a pregnant woman during the first trimester. While individual epidemiological studies on the association between PAXIL use and cardiac malformations have reported inconsistent findings, some meta-analyses of epidemiological studies have identified an increased risk of cardiovascular malformations (*see Data*).

Also, consider the risks of untreated depression when discontinuing or changing treatment with antidepressant drugs during pregnancy and the postpartum period pregnancy (*see Clinical Considerations*).

No evidence of treatment related malformations was observed in animal reproduction studies, when paroxetine was administered during the period of organogenesis at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits. These doses in rats are approximately 8 times the maximum recommended human dose (MRHD – 60 mg) and in rabbits less than 2 MRHD) on an mg/m² basis. When paroxetine was administered to female rats during the last trimester of gestation and continued through lactation, there was an increase in the number of pup deaths during the first four days of lactation. This effect occurred at a dose of 1 mg/kg/day which is less than the MRHD on an mg/m² basis (*see Data*).

The estimated background risks of major birth defects and miscarriage in pregnant adults with MDD, OCD, PD, SAD, GAD, or PTSD are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/fetal Risk: Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective longitudinal study of 201 pregnant women with a history of MDD who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risks of untreated depression when discontinuing or changing treatment with antidepressants during pregnancy and the postpartum period.

Maternal Adverse Reactions: Use of PAXIL in the month before delivery may be associated with an increased risk of postpartum hemorrhage [see *Warnings and Precautions (5.5)*].

Fetal/Neonatal Adverse Reactions: Neonates of mothers exposed to PAXIL and other SSRIs 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, tremors, jitteriness, irritability, and constant crying. These findings are consistent with either a direct toxic effect of SSRIs or possibly a drug discontinuation syndrome. In some cases, the clinical picture was consistent with serotonin syndrome [see *Warnings and Precautions (5.4)*].

Data

Human Data: Published epidemiological studies on the association between first trimester paroxetine use and cardiovascular malformations have reported inconsistent results; however, meta-analyses of population-based cohort studies published between 1996-2017 indicate a less than 2-fold increased risk for overall cardiovascular malformations.

- Specific cardiac malformations identified in two meta-analyses include approximately 2 to 2.5-fold increased risk for right ventricular outflow tract defects.
- One meta-analysis also identified an increased risk (less than 2-fold) for bulbus cordis anomalies and anomalies of cardiac septal closure, and an increased risk for atrial septal defects (pooled OR 2.38, 95% CI 1.14-4.97).

Important limitations of these studies included in these meta-analyses include potential confounding by indication, depression severity, and potential exposure misclassification.

Exposure to SSRIs, particularly later in pregnancy, may have an increased risk for PPHN. PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality.

Animal Data: Reproduction studies were performed at paroxetine doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 times (rat) and less than 2 times (rabbit) the maximum recommended human dose (MRHD – 60 mg) of PAXIL on an mg/m² basis. These studies 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 less than the MRHD on an mg/m² basis. The no effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

8.2 Lactation

Risk Summary

Data from the published literature report the presence of paroxetine in human milk (*see Data*). There are reports of agitation, irritability, poor feeding and poor weight gain in infants exposed to paroxetine through breast milk (*see Clinical Considerations*). There are no data on the effect of paroxetine on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXIL and any potential adverse effects on the breastfed child from PAXIL or from underlying maternal condition.

Clinical Considerations

Infants exposed to PAXIL through breastfeeding should be monitored for agitation, irritability, poor feeding and poor weight gain.

Data

Published literature suggests the presence of paroxetine in human milk with relative infant doses ranging between 0.4% to 2.2%, and a milk/plasma ratio of <1. No significant amounts of paroxetine were detected in the plasma of infants after breastfeeding.

8.3 Females and Males of Reproductive Potential

Infertility

Male: Based on findings from clinical studies, paroxetine may affect sperm quality which may impair fertility; it is not known if this effect is reversible [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of PAXIL in pediatric patients have not been established. Safety and effectiveness of PAXIL for the treatment of MDD in pediatric patients 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 pediatric patients.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse reactions were reported in at least 2% of PAXIL-treated pediatric patients and occurred at a rate at least twice that for placebo-treated pediatric patients: 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 (occurred in at least 2% of PAXIL-treated patients and at a rate at least twice that of placebo-treated patients) in the

pediatric clinical trials that included a taper phase regimen were emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain.

8.5 Geriatric Use

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)*].

In premarketing clinical trials with PAXIL, 17% of PAXIL-treated patients (approximately 700) were 65 years of age or older. Clinical studies of PAXIL did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients. The minimum plasma concentration (C_{min}) of paroxetine was higher in PAXIL-treated patients 65 years of age and older compared to younger adult patients [*see Clinical Pharmacology (12.3)*]; therefore, the starting recommended dosage is lower in patients 65 years of age and older with MDD, OCD, PTSD, and SAD and the maximum recommended dosage of PAXIL is lower in patients 65 years of age and older with MDD, OCD, PD, PTSD, SAD, and GAD [*see Dosage and Administration (2)*].

8.6 Renal Impairment

Compared to those without renal impairment (RI), paroxetine plasma concentrations in patients with RI were increased, which may increase the risk of paroxetine-associated adverse reactions. Paroxetine plasma concentrations were higher in patients with greater degrees of RI.

The recommended starting and maximum dosage of PAXIL is lower in patients with severe RI compared to those without RI [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*]. The recommended PAXIL dosage in patients with mild RI or moderate RI is the same as in those without RI.

8.7 Hepatic Impairment

Compared to those without hepatic impairment (HI), paroxetine plasma concentrations in patients with severe hepatic impairment (HI) were increased, which may increase the risk of paroxetine-associated adverse reactions.

The recommended starting and maximum dosage of PAXIL is lower in patients with severe HI compared to those without HI [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)*]. The recommended dosage in patients with mild or moderate HI is the same as in those without HI.

9 ABUSE AND DEPENDENCE

9.1 Controlled Substance

PAXIL contains paroxetine, which is not a controlled substance.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, included 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 [see *Warnings and Precautions* (5.7)].

10 OVERDOSAGE

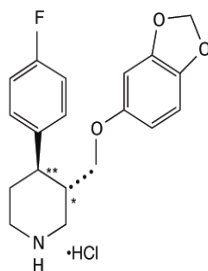
The following overdose complications have been reported with paroxetine overdose:

- 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 concomitant products including alcohol.
- Serotonin syndrome (patients with a multiple drug overdose with other proserotonergic drugs may have a higher risk).

If an overdose occurs, consider contacting a Poison Help Line (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 $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. 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 (paroxetine) tablets are for oral administration. Each 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 (paroxetine) oral suspension is for oral administration. Each 5 mL contains 10 mg of paroxetine equivalent to 11.1 mg of paroxetine hydrochloride. The oral suspension is not currently marketed.

Inactive ingredients consist of citric acid (anhydrous), FD&C yellow No. 6, flavorings, glycerin, methylparaben, microcrystalline cellulose and carboxymethylcellulose sodium, polacrillin 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 major depressive disorder (MDD), social anxiety disorder (SAD), obsessive compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD) and post-traumatic stress disorder (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 paroxetine dosage 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.

Cardiac Electrophysiology

At the maximum recommended paroxetine dose, a mean increase in the QTc interval >20 milliseconds is unlikely.

12.3 Pharmacokinetics

Nonlinearity in pharmacokinetics was observed with increasing dosage of PAXIL.

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

Absorption

Paroxetine was completely absorbed after oral dosing of a paroxetine solution of the hydrochloride salt. In a study in which healthy male subjects (n = 15) received 30 mg PAXIL tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it took substantially longer in some subjects. At steady state,

mean values of $C_{\max}$, $T_{\max}$, $C_{\min}$, and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hours (CV 10%), 30.7 ng/mL (CV 67%), and 21 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 one of the enzymes that metabolizes paroxetine is readily saturable.

Paroxetine has similar exposure after administration of the tablets and oral suspension.

Effect of Food: The effects of food on the bioavailability of paroxetine were studied in subjects who received a single PAXIL dose with and without food. AUC was slightly increased (6%) when PAXIL 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 [see *Dosage and Administration (2.1)*].

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 PAXIL tablets daily for 30 days.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at PAXIL 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 of PAXIL daily, values after 40 mg of PAXIL daily were only about 2 to 3 times greater than doubled.

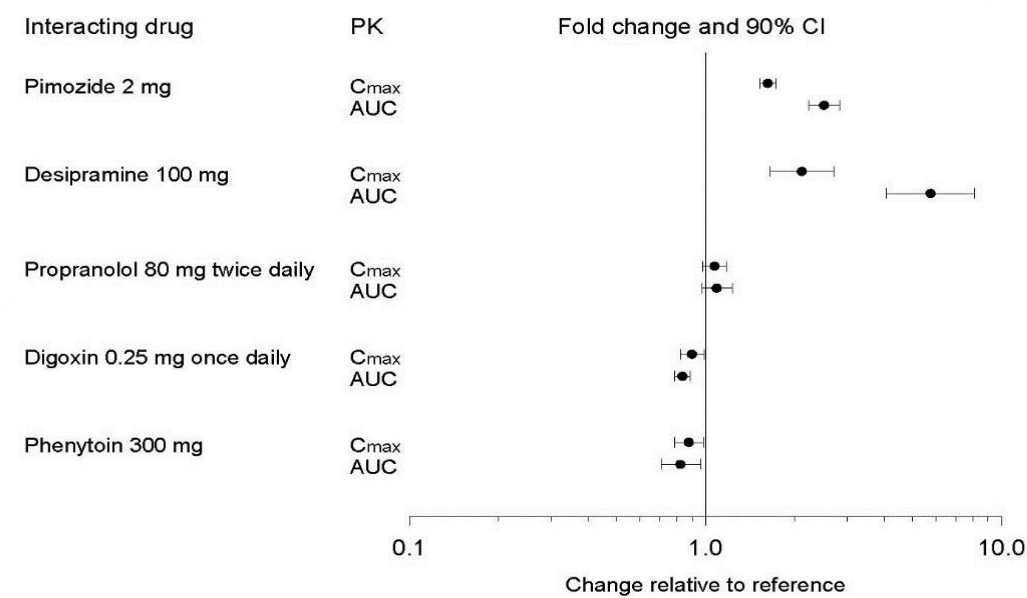
Paroxetine is extensively metabolized after oral PAXIL administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. 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 CYP2D6 at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of CYP2D6 in paroxetine metabolism increases the risk of drug interactions [see *Drug Interactions (7)*]. Pharmacokinetic characteristics of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (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

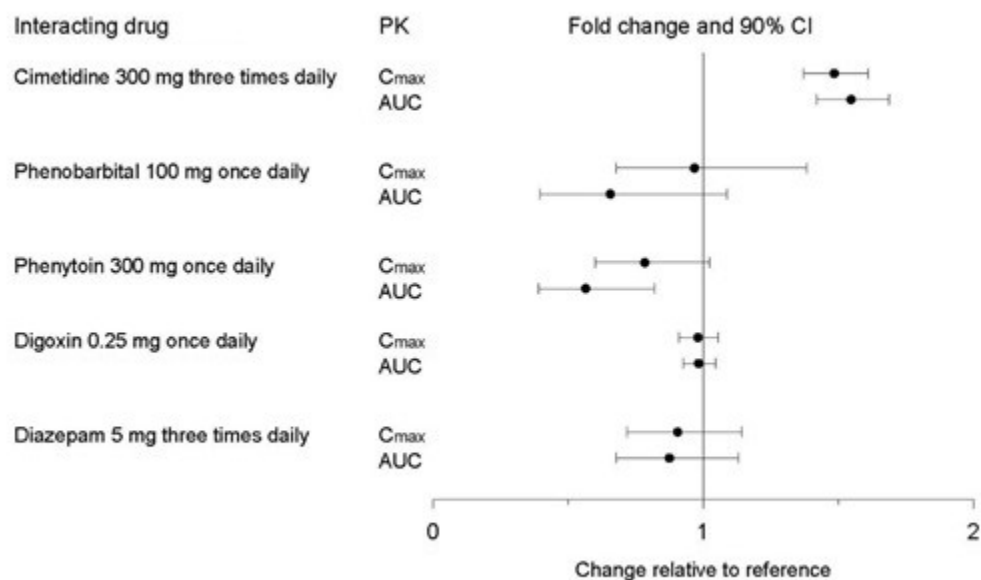
There are clinically significant, known drug interactions between PAXIL and other drugs [see *Drug Interactions (7)*]. See Figure 1 for the impact of paroxetine on the pharmacokinetics of concomitantly administered drugs and Figure 2 for the impact of other drugs on paroxetine pharmacokinetics.

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



Pimozide is a 3A4 moderate sensitive substrate and is a CYP2D6 substrate; desipramine is a 2D6 sensitive substrate; propranolol is a 2D6 moderate sensitive substrate, digoxin is P-gp substrate, and phenytoin is a 3A4 strong inhibitor.

Figure 2. Impact of Concomitantly Administered Drugs on the Pharmacokinetics of Paroxetine



Cimetidine is a OCT2, MATE1, and MATE2-K inhibitor, phenobarbital is a 3A4 moderate inducer, phenytoin is a 3A4 strong inhibitor, digoxin is P-gp substrate, and diazepam is a 2C19 moderate sensitive substrate. The increased paroxetine exposure after concomitant use of PAXIL with cimetidine is not expected to be clinically significant.

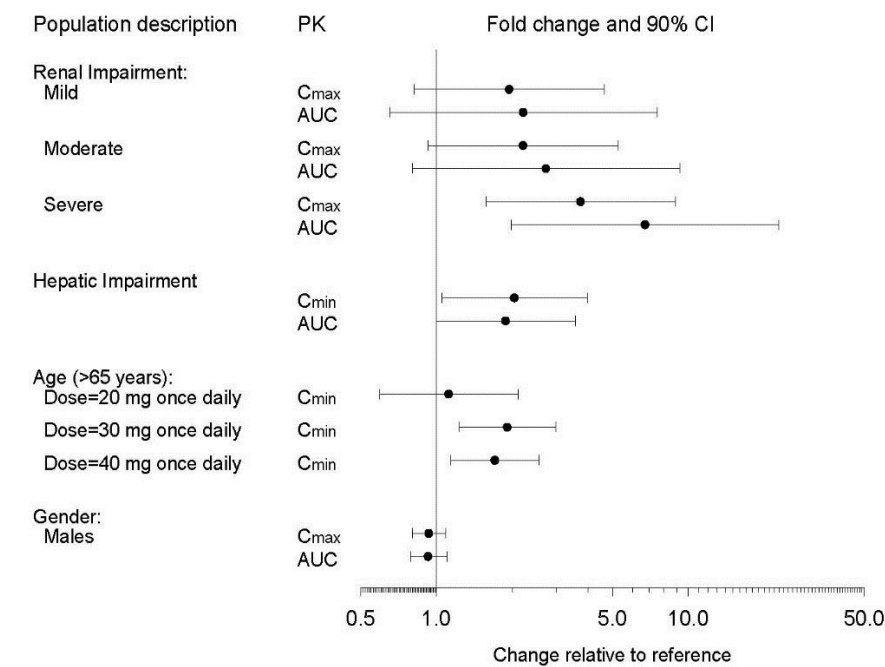
Theophylline: Reports of elevated theophylline levels associated with PAXIL treatment have been reported.

Drugs Metabolized by Cytochrome CYP3A4: An *in vivo* interaction study involving the concomitant use of steady-state paroxetine and a substrate for CYP3A4, revealed no effect of paroxetine on pharmacokinetics of the CYP3A4 substrate. In addition, *in vitro* studies have shown ketoconazole, a severe CYP3A4 inhibitor activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for CYP3A4, including triazolam and cyclosporine. Paroxetine's extent of CYP3A4 inhibition 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. Although the AUC and C_{max} was higher in patients with mild renal impairment (RI) or moderate RI compared to those without RI, there was a lot of variability in the exposure and the clinical significance of these findings are unknown [see *Use in Specific Populations* (8.6)]. For recommendations for use of PAXIL in geriatric patients, patients with severe hepatic impairment, or severe hepatic impairment, see *Use in Specific Populations* (8.5, 8.6, and 8.7), respectively.

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 in mice and 1, 5, and 20 mg/kg/day in rats. In mice, these doses were up to 2 times the MRHD of PAXIL 60 mg on a mg/m² basis and in rats 3.2 times the MRHD . 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 [see *Use in Specific Populations* (8.3)].

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/m² 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/m² basis).

14 CLINICAL STUDIES

14.1 Clinical Studies in Major Depressive Disorder

The efficacy of PAXIL for the treatment for major depressive disorder (MDD) in adults was established in 6 six-week, placebo-controlled studies of patients with MDD (aged 18 to 73) (Study MDD-1, MDD-2, MDD-3, MDD-4, MDD-5, and MDD-6). In these studies, PAXIL treatment was shown to be statistically significantly more effective than placebo treatment 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 treatment was statistically significantly better than placebo treatment 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 adults was demonstrated in a randomized withdrawal study in adult outpatients (Study MDD-7). Patients who responded to PAXIL treatment (HDRS total score <8) during an initial 8-week open-label treatment phase were then randomized to continue PAXIL or placebo treatment, for up to 1 year. Patients treated with PAXIL demonstrated a statistically significant lower relapse rate during the withdrawal phase (15%) compared to those treated with placebo (39%). Effectiveness was similar for male and female patients.

14.2 Clinical Studies in Obsessive Compulsive Disorder

The effectiveness of PAXIL in the treatment of obsessive-compulsive disorder (OCD) in adults was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies OCD-1 and OCD-2). In these studies, patients had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score that ranged from 23 to 26.

- In Study OCD-1, a dose-range finding study, patients received fixed daily doses of PAXIL 20 mg, 40 mg, or 60 mg. Study OCD-1 demonstrated that daily doses of PAXIL 40 mg and 60 mg were effective in the treatment of OCD in adults. Patients who received PAXIL 40 mg and 60 mg once daily 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 in those that received 20 mg once daily and a 3-point reduction in those that received placebo.
- Study OCD-2 was a flexible-dose study that compared PAXIL 20 mg to 60 mg daily with clomipramine 25 mg to 250 mg daily or placebo). In Study OCD-2, patients who received 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 patients who received placebo.

Table 10 describes the outcome classification by treatment group on Global Improvement items of the Clinical Global Impression (CGI) scale in Study OCD-1. Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or sex.

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

Outcome Classification	Placebo (n = 74)	PAXIL 20 mg Once Daily (n = 75)	PAXIL 40 mg Once Daily (n = 66)	PAXIL 60 mg Once Daily (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%

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

14.3 Clinical Studies in Panic Disorder

The effectiveness of PAXIL in the treatment of panic disorder (PD) in adults was demonstrated in three 10- to 12-week multicenter, placebo-controlled studies of adult outpatients (Studies PD-1, PD-2, and PD-3). Patients had PD (DSM-III-R), with or without agoraphobia. In these studies, PAXIL treatment was shown to be statistically significantly more effective than placebo treatment 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 PD-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 daily. A statistically significant difference from placebo was observed only for the PAXIL 40 mg daily group. At endpoint, 76% of patients who received PAXIL 40 mg daily were free of panic attacks, compared to 44% of patients who received placebo.
- Study PD-2 was a 12-week flexible-dose study that comparing PAXIL 10 mg to 60 mg daily and placebo daily. At endpoint, 51% of PAXIL-treated patients were free of panic attacks compared to 32% of placebo-treated patients.
- Study PD-3 was a 12-week flexible-dose study that compared PAXIL 10 mg to 60 mg daily to placebo daily in patients who concurrently received 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 PD-2 and PD-3, the mean PAXIL dosage for completers at endpoint was approximately 40 mg daily.

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

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

14.4 Clinical Studies in Social Anxiety Disorder

The effectiveness of PAXIL in the treatment of social anxiety disorder (SAD) in adults was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies SAD-1, SAD-2, and SAD-3) in adult outpatients with SAD (DSM-IV). In these studies, the effectiveness of PAXIL compared to placebo was evaluated based on the:

1. 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 SAD-1 and SAD-2 were flexible-dose studies that randomized adult patients with SAD to PAXIL or placebo once daily. Patients in the PAXIL group received 20 mg once daily. After two weeks of treatment, patients could be titrated up in increments of 10 mg per week to a maximum of PAXIL 50 mg once daily. The mean PAXIL dosage for completers was 41 mg once daily and 35 mg once daily in Studies SAD-1 and SAD-2, respectively. PAXIL treatment demonstrated statistically significant superiority over placebo treatment on both the CGI Improvement responder criterion and the LSAS.

- In Study SAD-1, for patients who completed week 12, 69% of PAXIL-treated patients compared to 29% of placebo-treated patients were CGI Improvement responders.
- In Study SAD-2, CGI Improvement responders were 77% and 42% for the PAXIL-treated and placebo-treated patients, respectively.

Study SAD-3 was a 12-week study that compared fixed doses of PAXIL 20 mg, 40 mg, or 60 mg once daily with placebo once daily. Patients in the:

- 20 mg once daily group received 20 mg once daily.
- 40 mg once daily group received 20 mg once daily for one week and then 40 mg once daily thereafter.
- 60 mg once daily group received 20 mg once daily for one week, 40 mg once daily for one week, and then 60 mg once daily thereafter.

The mean PAXIL dosage in the trial was 35 mg once daily.

PAXIL 20 mg once daily treatment was statistically significantly superior to placebo treatment 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 dosage groups. There was no indication in Study SAD-3 of any additional benefit for a PAXIL dosage higher than 20 mg daily.

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

14.5 Clinical Studies in Generalized Anxiety Disorder

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

- Study GAD-1 was an 8-week study that compared fixed doses of PAXIL 20 mg once daily and PAXIL 40 mg once daily with placebo once daily. Patients in the:
 - PAXIL 20 mg group, initially received PAXIL 10 mg once daily and after one week received 20 mg once daily.
 - PAXIL 40 mg group, initially received PAXIL 10 mg once daily for one week and then their dosage was increased by 10 mg per week until the target dosage of 40 mg once daily.

PAXIL dosages of 20 mg or 40 mg once daily 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 Study GAD-1 to suggest a greater benefit for the PAXIL 40 mg once daily dosage compared to the 20 mg daily dosage.

- Study GAD-2 was a flexible-dose study that compared PAXIL 20 mg to 50 mg once daily and placebo once daily. Patients in the PAXIL group started 10 mg once daily and after one week their dosage was increased to 20 mg once daily. Subsequently, their PAXIL dosage could be increased by weekly increments of 10 mg per day up to a maximum of 50 mg once daily. PAXIL demonstrated a statistically significant superiority over placebo on HAM-A total score.

A third study, a flexible-dose study (Study GAD-3) that compared PAXIL 20 mg to 50 mg once daily to placebo once daily, did not demonstrate statistically significant superiority of PAXIL over placebo on the 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 patients 65 years of age or older to conduct subgroup analyses on the basis of age.

In a long-term, randomized-withdrawal trial (Study GAD-4), 566 patients who met DSM-IV criteria for GAD, who had responded during a single-blind, 8-week acute treatment phase with PAXIL 20 mg to 50 mg once daily, were randomized to continue PAXIL at their same dosage, or

to switch to placebo treatment, 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 .
- 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 who were randomized to receive PAXIL experienced a statistically significantly lower relapse rate over the subsequent 24 weeks compared to those who were randomized to receive placebo.

14.6 Clinical Studies in Posttraumatic Stress Disorder

The effectiveness of PAXIL in the treatment of Posttraumatic Stress Disorder (PTSD) in adults was demonstrated in two 12-week, multicenter, placebo-controlled studies (Studies PTSD-1 and PTSD-2) of adult outpatients who met DSM-IV criteria for PTSD. The mean duration of PTSD symptoms for the two pooled studies was 13 years (ranged from 0.1 year to 57 years). The percentage of patients with secondary MDD or non-PTSD anxiety disorders in the two pooled studies was 41% (356 out of 858 patients) and 40% (345 out of 858 patients), respectively. Study outcomes were assessed by the:

1. Clinician-Administered PTSD Scale Part 2 (CAPS-2) score (the CAPS-2 score is a multi-item instrument that measures 3 aspects of PTSD with the following symptom clusters: Reexperiencing/intrusion, avoidance/numbing and hyperarousal), and
2. Clinical Global Impression-Global Improvement Scale (CGI-I).

The two 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 that had a score of 1 (very much improved) or 2 (much improved).

Below are the design characteristics and efficacy results from these studies:

- Study PTSD-1 was a 12-week study that compared fixed dosage regimen of PAXIL 20 mg or 40 mg daily to placebo daily. The PAXIL 20 mg and 40 mg dosage regimens 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 PAXIL dosage compared to the 20 mg daily PAXIL dosage. Study PTSD-2 was a 12-week flexible-dose study compared PAXIL 20 mg to 50 mg daily to placebo daily. 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.

In Study PTSD-1, 68% (377/551) of the patients were women, and in Study PTSD-2 66% (202/303) of the patient were women. Subgroup analyses did not indicate differences in treatment outcomes as a function of sex. There were an insufficient number of patients who were 65 years and older or among the racial groups to conduct subgroup analyses based on age or race, respectively.

A third study, a flexible-dose study (Study PTSD-3) that compared 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

PAXIL (paroxetine) Tablets

PAXIL (paroxetine) tablets are oval shaped (see Table 11 for the identifying characteristics of the PAXIL tablets strengths and package configurations).

Table 11: Identifying Characteristics of the PAXIL Tablets Strengths and Package Configurations

Tablet Strength	Color	Engraved Descriptors	Package Configuration	NDC Number
10 mg	yellow	Functionally scored, “PAXIL” on front and “10” on back	Bottles of 30	NDC 60505-4517-3
20 mg	pink	Functionally 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

10 mg/5 mL in bottles containing 250 mL of paroxetine (orange color and flavor) (NDC 60505-0402-5). The oral suspension is not currently marketed.

Store oral 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 suicidal thoughts and behaviors, especially early during PAXIL treatment and when the dosage is adjusted up or down, and instruct them to report such symptoms to the healthcare provider [*see 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. 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)*].

Potential for Drug Interactions with Concomitant Drugs

Advise patients to inform their health care provider if they are taking, or plan to take, any prescription or nonprescription drugs, since there is a potential for drug-drug interactions [*see Warnings and Precautions (5.3, 5.12) and Drug Interactions (7)*].

Increased Risk of Bleeding

Inform patients that the concomitant use of PAXIL with aspirin, NSAIDs, other antiplatelet drugs, warfarin, or other anticoagulants 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 nonprescription drugs 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 their 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 (5.11)*].

Embryo-Fetal Toxicity

Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with PAXIL. Advise women of the risks of PAXIL associated with [*see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)*]:

- First trimester use.
- Third trimester use including an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN).

Advise women of the risks associated with untreated depression in pregnancy in those being treated for MDD.

Advise women of the availability of a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PAXIL during pregnancy.

Lactation

Advise breastfeeding women using PAXIL to monitor infants for agitation, irritability, poor feeding and poor weight gain and to seek medical care if they notice these signs [*see Use in Specific Populations (8.2)*].

Males of Reproductive Potential

Advise men that PAXIL may affect sperm quality, which may impair fertility; it is unknown if this effect is reversible [*see Use in Specific Populations (8.3)*]

Hypersensitivity Reactions

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

Administration Information for Oral Suspension

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

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

Manufactured for:

Apotex Corp.

Weston, Florida USA 33326

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PAXIL® (PAX-il) (paroxetine) tablets, for oral use	MEDICATION GUIDE	PAXIL® (PAX-IL) (paroxetine) 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 and actions. PAXIL and other antidepressant medicines may increase the risk of suicidal thoughts and actions in 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 or 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 dose is changed. ○ Tell 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. Tell your healthcare provider between visits as needed, especially if you have concerns about symptoms. Tell your healthcare provider or get emergency medical help right away if you develop any of the following symptoms, especially if they are new, worse, or worry you: ○ suicide attempts ○ acting aggressive or violent ○ new or worse depression ○ feeling agitated, restless, angry, or irritable ○ an increase in activity or 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 See “What are the possible side effects of PAXIL?” for more information about side effects.		
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) It is not known if PAXIL is safe and effective in children.		
Who should not take PAXIL? Do not take PAXIL if you: • are taking, or have stopped taking within the last 14 days, a medicine called a monoamine oxidase inhibitor (MAOI), including the antibiotic linezolid or intravenous methylene blue • are taking certain medicines that can cause a heart rhythm problem called QT prolongation • 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. 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 high pressure in the eye (glaucoma) • have low sodium levels in your blood • have bone problems • have kidney or liver problems • are pregnant or plan to become pregnant. PAXIL can harm your unborn baby.		

- Taking PAXIL during your first trimester of pregnancy may cause your baby to be at an increased risk of having a heart problem (cardiac malformations) at birth.
- Taking PAXIL during your third trimester of pregnancy may cause your baby to have breathing, temperature, and feeding problems, low muscle tone, and irritability after birth and may cause your baby to be at an increased risk of a serious lung problem at birth. Talk to your healthcare provider about the risks to your unborn baby if you take PAXIL during pregnancy.
- You may be at increased risk for bleeding after childbirth if you take PAXIL in the month before delivery.
- Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with PAXIL.
- There is a pregnancy registry for women who are exposed to PAXIL during pregnancy. The purpose of the registry is to collect information about the health of women exposed to PAXIL and their baby. If you become pregnant during treatment with PAXIL, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or visit online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>.
- 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.
 - If you breastfeed during treatment with PAXIL, tell your healthcare provider if your baby develops agitation, irritability, poor feeding, or poor weight gain.

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 that can increase your risk for developing a serious problem called serotonin syndrome, including:
 - medicines used to treat migraine headaches called triptans
 - medicines used to treat mood, anxiety, psychotic or thought disorders, including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), MAOIs, tricyclic antidepressants, lithium, buspirone
 - tramadol, fentanyl, meperidine, methadone, or other opioids
 - tryptophan
 - amphetamines
 - St. John's Wort
- medicines that can affect blood clotting such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, or other blood thinners
- 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 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.
- Take PAXIL 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 healthcare provider or poison help line 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?”** and **“Especially tell your healthcare provider if you take:”** Tell your healthcare provider or go to the nearest hospital emergency room right away if you develop 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 that can lead to heart rhythm problems.** Taking PAXIL with certain other medicines may increase the risk of developing a serious heart problem called QT prolongation. See **“Who should not take PAXIL?”**
 - **Increased risk of bleeding.** Taking PAXIL with aspirin, NSAIDs, warfarin or other 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. Tell your healthcare provider if you develop any symptoms of mania, which 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 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)
 - shaking (tremor)
 - anxiety
 - confusion
 - headache
 - tiredness
 - problems sleeping
 - hypomania
 - ringing in your ears (tinnitus)
 - seizures
 - **Seizures (convulsions).**
 - **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. Tell your healthcare provider if you develop eye pain, changes in your vision, or swelling or redness in or around the eye.
 - **Low sodium levels in your blood (hyponatremia).** Low sodium levels in your blood that may be severe and may cause death, can happen during treatment with PAXIL. Elderly people and people who take diuretics or become dehydrated may be at a greater risk for this. Signs and symptoms may include:
 - headache
 - difficulty concentrating
 - memory changes
 - confusion
 - weakness and unsteadiness which can lead to falls
 - **In more severe or more sudden cases, signs and symptoms may include:**
 - seeing or hearing things that are not real (hallucinations)
 - fainting
 - seizures
 - coma
 - stopping breathing (respiratory arrest)
 - **Sexual problems (dysfunction).** Taking selective serotonin reuptake inhibitors (SSRIs), including PAXIL, 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. There may be treatments your healthcare provider can suggest.
 - **Bone fractures.**
- The most common side effects of PAXIL include:**
- male and female sexual function problems
 - weakness (asthenia)
 - constipation
 - decreased appetite
 - diarrhea
 - dizziness
 - problems sleeping
 - nausea
 - nervousness
 - sleepiness
 - sweating
 - shaking (tremor)

- dry mouth
- yawning
- infection

PAXIL may cause fertility problems in males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

Tell your healthcare provider or get emergency medical help right away if you develop an allergic reaction during treatment with PAXIL such as rash, hives, swelling, or difficulty breathing.

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 77°F (25°C).

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 pharmacist or healthcare provider for information about PAXIL that is written for health 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, polacrillin 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

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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