HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PEXEVA® (paroxetine mesylate) tablets, for oral use
Initial U.S. Approval: 1992

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

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

----------INDICATIONS AND USAGE----------

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

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Panic Disorder (PD)
- Generalized Anxiety Disorder (GAD)

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

- Recommended starting and maximum daily dosage: (2.2, 2.3, 2.4, 2.5)

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

- Elderly patients, patients with severe renal impairment or severe hepatic impairment: Starting dosage is 10mg/day. Maximum dosage is 40mg/day.
- When discontinuing PEXEVA, reduce dosage gradually (2.9)

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

- Tablets: 10 mg, 20 mg, 30 mg, 40 mg (3)

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

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

----------WARNINGS AND PRECAUTIONS----------

- *Serotonin Syndrome:* Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If occurs, discontinue PEXEVA and initiate supportive measures (5.2)
- *Embryofetal and Neonatal Toxicity:* Can cause fetal and neonatal harm. Increased risk of cardiovascular malformations for exposure during the first trimester. Exposure in late pregnancy may lead to an increased risk for persistent pulmonary hypertension (PPNH) of the newborn (5.4, 8.1)
- *Increased Risk of Bleeding:* Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, other antiplatelet drugs, warfarin, and other anticoagulant drugs may increase risk. (5.5)
- *Activation of Mania/Hypomania:* Screen for bipolar disorder (5.6)
- *Seizures:* Use with caution in patients with seizure disorders (5.8)
- *Angle-Closure Glaucoma:* Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5 .9)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 5% and at least twice placebo): asthenia, sweating, nausea, decreased appetite, dry mouth, constipation, somnolence, dizziness, insomnia, tremor, nervousness, libido decreased, female genital disorders, impotence, ejaculatory disturbance, other male genital disorders, orgasmic disturbance, and infection (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sebela Pharmaceuticals Inc. at 1-844-732-3521 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 PEXEVA or other protein-bound drugs (e.g., warfarin) as warranted (7)
- *Drugs Metabolized by CYP2D6:* Reduce dosage of drugs metabolized by CYP2D6 as warranted. (7)
- *Concomitant use with Tamoxifen:* Consider use of an alternative antidepressant with little or no CYP2D6 inhibition. (5.11, 7)

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 anti-depressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.1)]*. PEXEVA is not approved for use in pediatric patients [*see Use in Specific Populations (8.4)*].

1 INDICATIONS AND USAGE

PEXEVA is indicated in adults for the treatment of:

- Major depressive disorder (MDD)
- Obsessive-compulsive disorder (OCD)
- Panic disorder (PD)
- Generalized anxiety disorder (GAD)

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

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

2.2 Recommended Dosage

The recommended initial dosage and maximum dosage of PEXEVA in patients with MDD, OCD, PD, and GAD are presented in Table 1.

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

TABLE 1: Recommended Daily Dosage of PEXEVA in Patients with MDD, OCD, PD, and GAD

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

2.3 Screen for Bipolar Disorder Prior to Starting PEXEVA

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

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

The recommended initial dose is 10 mg/day for elderly patients, patients with severe renal impairment and patients with severe hepatic impairment. Dosage should not exceed 40 mg/day *[see Use in Specific Populations (8.5, 8.6)]*

2.5 Switching Patients to or from a Monoamine Oxidase Inhibitor Antidepressant

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

2.6 Discontinuation of Treatment with PEXEVA

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

3 DOSAGE FORMS AND STRENGTHS

PEXEVA is available as oval, film-coated tablets which contains paroxetine mesylate equivalent to paroxetine as follows:

10 mg tablets: white, oval, film-coated tablets, with the inscription “POT 10” on one side.

20 mg tablets: dark orange, oval, film-coated tablets, with the inscription “POT 20” on one side. The tablets are scored on both sides.

30 mg tablets: yellow, oval, film-coated tablets, with the inscription “POT 30” on one side.

40 mg tablets: rose, oval, film-coated tablets, with the inscription “POT 40” on one side.

4 CONTRAINDICATIONS

PEXEVA is contraindicated in patients:

- Taking, or within 14 days of stopping, MAOIs (including the MAOIs linezolid and intravenous methylene blue) because of an increased risk of serotonin syndrome *[see Warnings and Precautions (5.2), Drug Interaction (7)]*.
- Taking thioridazine because of risk of QT prolongation *[see Warnings and Precautions (5.3), Drug Interaction (7)]*.
- Taking pimozide because of risk of QT prolongation *[see Warnings and Precautions (5.3), Drug Interaction (7)]*.
- With known hypersensitivity (e.g., anaphylaxis, angioedema, Stevens-Johnson syndrome) to paroxetine or to any of the inactive ingredients in PEXEVA *[see Adverse Reactions (6.2, 6.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that include 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 placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

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

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

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond 4 months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication of 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 PEXEVA, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts and behaviors.

5.2 Serotonin Syndrome

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

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

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

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

5.3 Drug Interactions Leading to QT Prolongation

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

5.4 Embryofetal and Neonatal Toxicity

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

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

5.5 Increased Risk of Bleeding

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

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

5.6 Activation of Mania or Hypomania

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

5.7 Discontinuation Syndrome

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible *[see Dosage and Administration (2.X)]*.

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

During clinical trials of paroxetine in GAD and another indication, incremental decreases in the daily dose by 10 mg/day at weekly intervals followed by 1 week at 20 mg/day was used before treatment was discontinued. The following adverse reactions were reported at an incidence of 2% or greater for paroxetine and were at least twice that reported for placebo: Abnormal dreams, paresthesia, and dizziness.

5.8 Seizures

During clinical studies, seizure occurred in 0.1% of patients treated with PEXEVA. PEXEVA should be prescribed with caution in patients with a seizure disorder. Discontinue PEXEVA in any patient who develops seizures.

5.9 Angle-Closure Glaucoma

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

5.10 Hyponatremia

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

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

5.11 Reduction of Efficacy of Tamoxifen

Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 and lower blood levels of tamoxifen *[see Drug interactions (7.1).* One study suggests that the risk may increase with longer duration of coadministration. However, other studies have failed to demonstrate such a risk. It is uncertain whether the co-administration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

5.12 Bone Fracture

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

6 ADVERSE REACTIONS

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

- Hypersensitivity reactions to paroxetine *[see Contraindications (4)]*
- Suicidal Thoughts and Behaviors *[see Warnings and Precautions (5.1)]*
- Serotonin syndrome *[see Warnings and Precautions (5.2)]*
- Embryofetal and Neonatal Toxicity *[see Warnings and Precautions (5.4)]*
- Increased Risk of Bleeding *[see Warnings and Precautions (5.5)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.6)]*
- Discontinuation Syndrome *[see Warnings and Precautions (5.7)]*
- Seizure *[see Warnings and Precautions (5.7)]*
- Angle-closure Glaucoma *[see Warnings and Precautions (5.9)]*
- Hyponatremia *[see Warnings and Precautions (5.10)]*
- Bone 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 directly be compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data for paroxetine are from:

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

Adverse Reactions Leading to Discontinuation

Twenty percent (1199/6145) of patients treated with paroxetine in clinical trials in MDD and 11.8% (64/542), 9.4% (44/469), and 10.7% (79/735) of patients treated with paroxetine in clinical trials in OCD, PD, and GAD, respectively, discontinued treatment due to an adverse reaction. Table 3 shows the most

common reactions (≥1%) associated with discontinuation and considered to be drug related (i.e., those reactions associated with dropout at a rate approximately twice or greater for paroxetine compared to placebo).

TABLE 3: Adverse Reactions Reported as Leading to Discontinuation (≥1% of Paroxetine-Treated Patients and (≥2% Placebo) in MDD, OCD, PD, and GAD Trials

	MDD		OCD		PD		GAD	
	Paroxetine %	Placebo %	Paroxetine %	Placebo %	Paroxetine %	Placebo %	Paroxetine %	Placebo %
CNS								
Somnolence	2.3	0.7	-	-	1.9	0.3	2.0	0.2
Insomnia	-	-	1.7	0	1.3	0.3	-	-
Agitation	1.1	0.5	-	-	-	-	-	-
Tremor	1.1	0.3	-					
Dizziness	-	-	1.5	0	-	-	1.0	0.2
Gastrointestinal								
Constipation	-	-	1.1	0	-	-	-	-
Nausea	3.2	1.1	1.9	0	3.2	1.2	2.0	0.2
Diarrhea	1.0	0.3	-	-	-	-	-	-
Dry mouth	1.0	0.3	-	-	-	-	-	-
Vomiting	1.0	0.3	-	-	-	-	-	-
Other								
Asthenia	1.6	0.4	1.9	0.4	-	-	1.8	0.2
Abnormal Ejaculation [1]	1.6	0	2.1	0	-	-	2.5	0.5
Sweating	1.0	0.3	-	-	-	-	1.1	0.2
Impotence [1]	-	-	1.5	0	-	-	-	-

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

[1] Incidence corrected for gender.

Most Common Adverse Reactions in MDD, OCD, PD, and GAD

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

Major Depressive Disorder: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

Obsessive Compulsive Disorder: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

Panic Disorder: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

Generalized Anxiety Disorder: asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Adverse Reactions Occurring at an Incidence of 1% or More in Paroxetine Treated Patients

Major Depressive Disorder: Table 3 enumerates adverse reactions that occurred at an incidence of 1% or more and greater than placebo in clinical trials of paroxetine-treated patients with MDD.

TABLE 4: Adverse Reactions (≥1% of Paroxetine-treated Patients and Greater than Placebo) in 6-Week Clinical Trials for MDD

Body System	Preferred Term	Paroxetine (n=421) %	Placebo (n=421) %
Body as a Whole	Headache	18	17
	Asthenia	15	6
Cardiovascular	Palpitation	3	1
	Vasodilation	3	1
Dermatologic	Sweating	11	2
	Rash	2	1
Gastrointestinal	Nausea	26	9
	Dry Mouth	18	12
	Constipation	14	9
	Diarrhea	12	8
	Decreased Appetite	6	2
	Flatulence	4	2
	Oropharynx Disorder [1]	2	0
	Dyspepsia	2	1
Musculoskeletal	Myopathy	2	1
	Myalgia	2	1
	Myasthenia	1	0
Nervous System	Somnolence	23	9

	Dizziness	13	6
	Insomnia	13	6
	Tremor	8	2
	Nervousness	5	3
	Anxiety	5	3
	Paresthesia	4	2
	Libido Decreased	3	0
	Drugged Feeling	2	1
	Confusion	1	0
Respiration	Yawn	4	0
Special Senses	Blurred Vision	4	1
	Taste Perversion	2	0
Urogenital System	Ejaculatory Disturbance [2,3]	13	0
	Other Male Genital Disorders [2,4]	10	0
	Urinary Frequency	3	1
	Urination Disorder [5]	3	0
	Female Genital Disorders [2,6]	2	0

[1] Includes mostly "lump in throat" and "tightness in throat."

[2] Percentage corrected for gender.

[3] Mostly "ejaculatory delay."

[4] Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction" and "impotence."

[5] Includes mostly "difficulty with micturition" and "urinary hesitancy."

[6] Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Obsessive Compulsive Disorder and Panic Disorder: Table 5 enumerates adverse reactions that occurred at a frequency of 2% or more in clinical trials in patients with OCD and PD.

TABLE 5: Adverse Reactions (≥2% of Paroxetine-Treated Patients and Greater than Placebo) in 10- to 12-Week Clinical Trials for OCD and PD

		Obsessive Compulsive Disorder		Panic Disorder	
Body System	**Preferred Term**	**Paroxetine (n=542) %**	**Placebo (n=265) %**	**Paroxetine (n=469) %**	**Placebo (n=324) %**
Body as a Whole	Asthenia	22	14	14	5
	Abdominal Pain	-	-	4	3
	Chest Pain	3	2	-	-
	Back Pain	-	-	3	2
	Chills	2	1	2	1
Cardiovascular	Vasodilation	4	1	-	-
	Palpitation	2	0	-	-
Dermatologic	Sweating	9	3	14	6
	Rash	3	2	-	-
Gastrointestinal	Nausea	23	10	23	17
	Dry Mouth	18	9	18	11
	Constipation	16	6	8	5
	Diarrhea	10	10	12	7
	Decreased Appetite	9	3	7	3
	Increased Appetite	4	3	2	1
Nervous System	Insomnia	24	13	18	10
	Somnolence	24	7	19	11
	Dizziness	12	6	14	10
	Tremor	11	1	9	1
	Nervousness	9	8	-	-
	Libido Decreased	7	4	9	1
	Agitation	-	-	5	4
	Anxiety	-	-	5	4
	Abnormal Dreams	4	1	-	-
	Concentration Impaired	3	2	-	-
	Depersonalization	3	0	-	-
	Myoclonus	3	0	3	2
	Amnesia	2	1	-	-
Respiratory System	Rhinitis	-	-	3	0
Special Senses	Abnormal Vision	4	2	-	-
	Taste Perversion	2	0	-	-
Urogenital System	Abnormal Ejaculation [1]	23	1	21	1
	Female Genital	3	0	9	1

Disorder [1]				
Impotence [1]	8	1	5	0
Urinary Frequency	3	1	2	0
Urination Impaired	3	0	-	-
Urinary Tract Infection	2	1	2	1

[1] Percentage corrected for gender.

Generalized Anxiety Disorder: Table 6 enumerates adverse reactions that occurred at a frequency of 2% or more among GAD patients on paroxetine who participated in placebo-controlled trials of 8-weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day.

TABLE 6: Adverse Reactions (≥2% of Paroxetine-Treated Patients and Greater than Placebo) in 8-Week Clinical Trials for GAD

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

[1] Percentage corrected for gender.

Dose Dependency of Adverse Reactions: A comparison of adverse reaction rates in a fixed-dose study comparing paroxetine 10, 20, 30, and 40 mg/day with placebo in the treatment of MDD revealed a clear dose dependency for some of the more common adverse reactions associated with paroxetine use, as shown in Table 7:

TABLE 7: Adverse Reactions (≥5% of Paroxetine-Treated Patients and Twice that of Placebo) in a Dose-Comparison Trial in the Treatment of MDD*

Body System/ Preferred Term	Placebo	Paroxetine			
	n=51 %	10 mg n=102 %	20 mg n=104 %	30 mg n=101 %	40 mg n=102 %
Body as a Whole					
Asthenia	0	2.9	10.6	13.9	12.7
Dermatology					
Sweating	2.0	1.0	6.7	8.9	11.8
Gastrointestinal					
Constipation	5.9	4.9	7.7	9.9	12.7
Decreased Appetite	2.0	2.0	5.8	4.0	4.9
Diarrhea	7.8	9.8	19.2	7.9	14.7
Dry Mouth	2.0	10.8	18.3	15.8	20.6
Nausea	13.7	14.7	26.9	34.7	36.3
Nervous System					
Anxiety	0	2.0	5.8	5.9	5.9
Dizziness	3.9	6.9	6.7	8.9	12.7
Nervousness	0	5.9	5.8	4.0	2.9
Paresthesia	0	2.9	1.0	5.0	5.9
Somnolence	7.8	12.7	18.3	20.8	21.6
Tremor	0	0	7.7	7.9	14.7
Special Senses					

Blurred Vision	2.0	2.9	2.9	2.0	7.8
Urogenital System					
Abnormal Ejaculation	0	5.8	6.5	10.6	13.0
Impotence	0	1.9	4.3	6.4	1.9
Male Genital Disorders	0	3.8	8.7	6.4	3.7

In a fixed-dose study comparing placebo and paroxetine 20, 40, and 60 mg in the treatment of OCD, there was no clear relationship between adverse reactions and the dose of paroxetine to which patients were assigned. No new adverse reactions were observed in the paroxetine 60 mg dose group compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and paroxetine 10, 20, and 40 mg in the treatment of PD, there was no clear relationship between adverse reactions and the dose of paroxetine to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse reactions were observed in patients receiving 60 mg of paroxetine compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 20 and 40 mg of paroxetine in the treatment of GAD, for most of the adverse reactions, there was no clear relationship between adverse reactions and the dose of paroxetine to which patients were assigned, except for the following adverse reactions: asthenia, constipation, and abnormal ejaculation. .

Male and Female Sexual Dysfunction

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of SSRI treatment. However, reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, 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 product labeling are likely to underestimate their actual incidence.

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

Table 8: Incidence of Sexual Adverse Reactions in Controlled Clinical Trials

	Paroxetine	**Placebo**
n (males)	**1446**	**1042**
	%	**%**
Decreased Libido	6 to 15	0 to 5
Ejaculatory Disturbance	13 to 28	0 to 2
Impotence	2 to 9	0 to 3
n (females)	**1822**	**1340**
	%	**%**
Decreased Libido	0 to 9	0 to 2
Orgasmic Disturbance	2 to 9	0 to 1

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

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

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, healthcare providers should routinely inquire about such possible side effects.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 0.2% of paroxetine-treated patients compared to 0.1% of patients receiving placebo.

6.2 Other Reactions Observed During the Premarketing Evaluation of Paroxetine

Less Common Adverse Reactions

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

Adverse reactions are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare adverse reactions are those occurring in fewer than 1/1000 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 infarction, 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, chlolelithiasis, 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, pyuria, polyuria, 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.

6.3 Postmarketing Experience

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

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

7 DRUG INTERACTIONS

7.1 Clinically Significant Drug Interactions

Table 9: Clinically Significant Drug Interactions with PEXEVA

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	The concomitant use of SSRIs, including PEXEVA, and MAOIs increases the risk of serotonin
Intervention	PEXEVA is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue *[see Dosage and Administration (2), Contraindications (4), Warnings and Precautions (5.2)]*.
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Pimozide and Thioridazine	
Clinical Impact	Increased plasma concentrations of pimozide and thioridazine, drugs with a narrow therapeutic index, may increase the risk of QTc prolongation and ventricular arrhythmias.
Intervention	PEXEVA is contraindicated in patients taking pimozide or thioridazine *[see Contraindications (4)]*.
Other Serotonergic Drugs	
Clinical Impact	The concomitant use of serotonergic drugs with PEXEVA increases the risk of serotonin syndrome.
Intervention	Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of PEXEVA and/or concomitant serotonergic drugs *[see Warnings and Precautions (5.2)]*.
Examples	other SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort
Drugs that Interfere with Hemostasis (antiplatelet agents and anticoagulants)	
Clinical Impact	The concurrent use of an antiplatelet agent or anticoagulant with PEXEVA may potentiate the risk of bleeding.
Intervention	Inform patients of the increased risk of bleeding associated with the concomitant use of PEXEVA and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio *[see Warnings and Precautions (5.5)]*.
Examples	aspirin, clopidogrel, heparin, warfarin

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy may have an increased risk of congenital malformations, particularly cardiovascular malformations. The findings from these studies are summarized below:

- A study based on Swedish national registry data demonstrated that infants exposed to paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular malformations (2% risk in paroxetine-exposed infants) compared to the entire registry population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No increase in the risk of overall congenital malformations was seen in the paroxetine-exposed infants. The cardiac malformations in the paroxetine-exposed infants were primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in severity from those that resolve spontaneously to those which require surgery.
- A separate retrospective cohort study from the United States (United Healthcare data) evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine (risk of 1.5%) compared to other antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study also suggested an increased risk of overall major congenital malformations including cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8).
- Two large case-control studies using separate databases, each with >9,000 birth defect cases and >4,000 controls, found that maternal use of paroxetine during the first trimester of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow tract obstructions. In one study the OR was 2.5 (95% confidence interval, 1.0 to 6.0, 7 exposed infants) and in the other study the OR was 3.3 (95% confidence interval, 1.3 to 8.8, 6 exposed infants).
- Other studies have found varying results as to whether there was an increased risk of overall, cardiovascular, or specific congenital malformations. A meta-analysis of epidemiological data over a 16-year period (1992 to 2008) included a total of 20 distinct studies: 11 studies (including the above noted studies) reported estimates for both cardiovascular defects and overall congenital malformations, 3 studies reported estimates only for cardiovascular defects, and 6 studies reported estimates only for overall congenital malformations. While subject to limitations, this meta-analysis suggested an increased occurrence of cardiovascular malformations (prevalence odds ratio [POR] 1.5; 95% confidence interval 1.2 to 1.9) and overall malformations (POR 1.2; 95% confidence interval 1.1 to 1.4) with paroxetine use during the first trimester. It was not possible in this meta-analysis to determine the extent to which cardiovascular malformations might have contributed to overall malformations, nor was it possible to determine whether any specific types of cardiovascular malformations contributed to all cardiovascular malformations.
- If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or

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

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD of 60 mg on an mg/m^2 basis. These studies have revealed no evidence of developmental effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day which is less than the MRHD on an mg/m^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

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

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use, including PEXEVA, in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with PEXEVA®, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

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

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

8.5 Geriatric Use

In premarketing clinical trials with immediate-release paroxetine, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; however, no overall differences in safety or effectiveness were observed between these subjects and younger subjects *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.

SSRIs, including PEXEVA, 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 (5.10)]*.

8.6 Renal and/or Hepatic Impairment

Increased plasma concentrations of paroxetine occur in patients with renal and hepatic impairment. The initial dosage of PEXEVA should be reduced in patients with severe renal impairment and patients with severe hepatic impairment *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Human Experience

Since the introduction of immediate-release paroxetine in the United States, spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide. These include overdoses with paroxetine alone and in combination with other substances. There are reports of fatalities that appear to involve paroxetine alone.

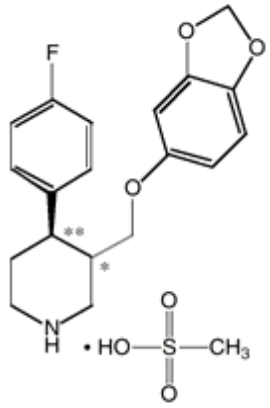
Commonly reported adverse reactions associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdose Management

No specific antidotes for paroxetine are known. If over-exposure occurs, call your poison control center at 1-800-222-1222 for latest recommendations.

11 DESCRIPTION

PEXEVA contains paroxetine mesylate, an SSRI. It is the mesylate salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine mesylate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$. The molecular weight is 425.5 (329.4 as free base). The structural formula is:



Paroxetine mesylate is an odorless, off-white powder, having a melting point range of 147° to 150°C and a solubility of more than 1 g/ml in water.

PEXEVA tablets are intended for oral administration. Each oval, film-coated tablet contains 10 mg, 20 mg, 30 mg, or 40 mg paroxetine equivalent to 12.9 mg, 25.8 mg, 38.8 mg, or 51.7 mg paroxetine mesylate, respectively. Inactive ingredients consist of dibasic calcium phosphate, hydroxypropyl methylcellulose, hydroxypropylcellulose, magnesium stearate, sodium starch glycolate, titanium dioxide, ferric oxide red (C.I. 77491) (20 mg and 40 mg only) and ferric oxide yellow (C.I. 77492) (20 mg, 30 mg, and 40 mg only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption

Paroxetine mesylate is completely absorbed after oral dosing of the mesylate salt. In a study in which normal male subjects (n=25) received paroxetine 30 mg tablets daily for 24 days, steady-state paroxetine concentrations were achieved by approximately 13 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of Cmax, Tmax, Cmin, and T1/2 were 81.3 ng/ml (CV 41%), 8.1 hr. (CV 56%), 43.2 ng/ml (CV 52%), and 33.2 hr. (CV 52%), respectively. The steady-state Cmax and Cmin values were about 7 and 10 times what would be predicted from single dose studies. Steady-state drug exposure based on AUC0-24 was about 10 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.

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

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

Effect of Food

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

Distribution

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma. Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/ml and 400 ng/ml, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/ml. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Elimination

Metabolism

The elimination half-life is approximately 15 to 20 hours after a single dose of PEXEVA.

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

Excretion

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

Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces.

Drug Interaction Studies:

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

Potential Effect of PEXEVA on Other Drugs

Drugs Metabolized by CYP3A4

An *in vivo* drug interaction study involving the co-administration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. *In vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for CYP3A4, including astemizole, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Drugs Metabolized by CYP2D6

Pimozide: Higher doses of paroxetine have been shown to elevate plasma levels of pimozide. In a controlled study of healthy volunteers, after paroxetine was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone *[see Drug Interactions (7.1)]*.

Tamoxifen: It is uncertain whether the co-administration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6. However, other studies have failed to demonstrate such a risk *[see Warnings and Precautions (5.11) and Drug Interactions (7.1)]*.

Desipramine: In one study, daily dosing of paroxetine (20 mg once daily) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively *[see Drug Interactions (7.1)]*.

Risperidone: Daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day), a CYP2D6 substrate, increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold *[see Drug Interactions (7.1)]*.

Atomoxetine: The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady-state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone *[see Drug Interactions (7.1)]*.

Digoxin: Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine *[see Drug Interactions (7.1)]*.

Beta Blockers: In a study in which propranolol (80 mg twice daily) was dosed orally for 18 days, the steady-state plasma concentrations of propranolol were unaltered during co-administration with paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated.

Potential Effect of Other Drugs on PEXEVA

Concomitant use of paroxetine with other drugs that alter CYP enzymes activities including CYP2D6 may affect the plasma concentrations of paroxetine. Specific studies investigating the effect of other drugs on paroxetine are listed below:

Cimetidine: Cimetidine inhibits many cytochrome P450 enzymes. In a study in which paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg three times daily) for the final week *[see Drug Interactions (7.2)]*.

Phenobarbital: Phenobarbital induces many cytochrome P450 enzymes. When a single oral 30 mg dose of paroxetine was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Because paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed *[see Drug Interactions (7.2)]*.

Phenytoin: When a single oral 30 mg dose of paroxetine was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Because both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed *[see Drug Interactions (7.2)]*.

Digoxin: A clinical drug interaction study showed that concurrent use of digoxin did not affect paroxetine exposure.

Diazepam: A clinical drug interaction study showed that concurrent use of diazepam did not affect paroxetine exposure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are 2.0 (mouse) and 3 (rat) times the maximum recommended human dose (MRHD) of 60 mg on a mg/m^2 basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

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

Impairment of Fertility**:** Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality during SSRI treatment, which may affect fertility in some men. A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2 times the MRHD of 60 mg on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (8 and 4 times the MRHD of 60 mg on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

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

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

14.2 Obsessive Compulsive Disorder

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

Table 10 provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impressions (CGI) scale for Study 1.

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

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

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

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

14.3 Panic Disorder

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

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

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

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

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

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

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

14.4 Generalized Anxiety Disorder

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

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

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets:

Pexeva (paroxetine mesylate) tablets are oval, film-coated tablets supplied as follows:

PEXEVA 10 mg white tablets with the inscription POT 10 on one side.

NDC 54766-201-01 Bottles of 30

PEXEVA 20 mg dark orange tablets with the inscription POT 20 on one side. The tablets are scored on both sides.

NDC 54766-202-01 Bottles of 30

30 mg yellow tablets with the inscription POT 30 on one side.

NDC 54766-203-01 Bottles of 30

40 mg rose tablets with the inscription POT 40 on one side.

NDC 54766-204-01 Bottles of 30

Protect from Humidity. Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature)

17 PATIENT COUNSELING INFORMATION

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

Suicidal Thoughts and Behaviors

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

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of PEXEVA with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also other, such as linezolid). Instruct patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome *[see Warnings and Precautions (5.2), Drug Interactions (7)]*.

Concomitant Medications

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

Increased Risk of Bleeding

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

Activation of Mania/Hypomania

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

Discontinuation Syndrome

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

Allergic Reactions

Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing *[see Adverse Reactions (6)]*.

Embryo-Fetal Toxicity

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

Nursing

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

Distributed By

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Toll Free 1-844-732-3521

Medication Guide

PEXEVA® (pex-EE-va)

(paroxetine mesylate)

tablets

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

PEXEVA can cause serious side effects, including:

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

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

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

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

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

What is PEXEVA?

PEXEVA 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)
- Generalized Anxiety Disorder (GAD)

Do not take PEXEVA if you:

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

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

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

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

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

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

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

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

Especially tell your healthcare provider if you take:

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

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

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

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 PEXEVA?

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

What are the possible side effects of PEXEVA?

PEXEVA can cause serious side effects, including:

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

- dizziness
- nausea, vomiting, diarrhea

- **Medicine interactions.** Taking PEXEVA with certain other medicines including thioridazine and pimozide may increase the risk of developing a serious heart problem called QT prolongation**.**
- **Abnormal bleeding.** Taking PEXEVA with aspirin, NSAIDs, or blood thinners may add to this risk. Tell your healthcare provider about any unusual bleeding or bruising.
- **Manic episodes.** Manic episodes may happen in people with bipolar disorder who take PEXEVA. Symptoms may include:
  - greatly increased energy
  - racing thoughts
  - unusually grand ideas
  - talking more or faster than usual
  - severe problems sleeping
  - reckless behavior
  - excessive happiness or irritability
- **Discontinuation syndrome.** Suddenly stopping PEXEVA may cause you to have serious side effects. Your healthcare provider may want to decrease your dose slowly. Symptoms may include:
  - nausea
  - sweating
  - changes in your mood
  - irritability and agitation
  - dizziness
  - electric shock feeling (paresthesia)
  - tremor
  - anxiety
  - confusion
  - headache
  - tiredness
  - problems sleeping
  - hypomania
  - ringing in your ears (tinnitus)
  - seizures
- **Seizures (convulsions).**
- **Eye problems (angle-closure glaucoma).** PEXEVA may cause a type of eye problem called angle-closure glaucoma in people with certain other eye conditions. Call your healthcare provider if you have 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 serious and may cause death, can happen during treatment with PEXEVA. Elderly people and people who take certain medicines may be at a greater risk for developing low sodium levels in your blood. Signs and symptoms may include:
  - headache
  - difficulty concentrating
  - memory changes
  - confusion
  - weakness and unsteadiness on your feet which can lead to falls

  In more severe or more sudden cases, signs and symptoms include:
  - seeing or hearing things that are not real (hallucinations)
  - fainting
  - seizures
  - coma
  - stopping breathing (respiratory arrest)
- **Bone fractures.**

The most common side effects of PEXEVA include:

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

These are not all the possible side effects of PEXEVA.

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 PEXEVA?

- Store PEXEVA at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep PEXEVA bottle closed tightly.
- **Keep PEXEVA and all medicines out of reach of children.**

General information about the safe and effective use of PEXEVA.

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

What are the ingredients in PEXEVA?

Active ingredient: paroxetine mesylate

Inactive ingredients: dibasic calcium phosphate, hydroxypropyl methylcellulose, hydroxypropylcellulose, magnesium stearate, sodium starch glycolate, titanium dioxide, and iron oxide(s).

Distributed by:
Sebela Pharmaceuticals Inc., 645 Hembree Parkway, Suite I, Roswell, GA 30076

For more information about PEXEVA call (1-844-732-3521) or go to www.PEXEVA.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised 12/2020

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