**PAROXETINE HYDROCHLORIDE- paroxetine hydrochloride tablet, film coated, extended release**
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**Apotex Corp**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use Paroxetine HCL CR safely and effectively. See full prescribing information for Paroxetine HCL CR.**
**PAROXETINE HCL CR (paroxetine) extended-release tablets, for oral use**
**Initial U.S. Approval: 1992**

**WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

***See full prescribing information for complete boxed warning.***

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

## RECENT MAJOR CHANGES

Warnings and Precautions (5.2 ,5.4, 5.5) 08/2023

## INDICATIONS AND USAGE

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

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

## DOSAGE AND ADMINISTRATION

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

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

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

## DOSAGE FORMS AND STRENGTHS

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

## CONTRAINDICATIONS

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

## WARNINGS AND PRECAUTIONS

- *Serotonin Syndrome:* Increased risk when co-administered with other serotonergic agents, but also when taken alone. If occurs, discontinue Paroxetine HCL CR and serotonergic agents and initiate supportive measures. (5.2)
- *Embryofetal Toxicity*: May cause fetal harm. Meta-analysis of epidemiological studies have shown increased risk (less than 2-fold) of cardiovascular malformations with exposure during the first trimester.(5.4, 8.1)
- *Increased Risk of Bleeding:* Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, other antiplatelet drugs, warfarin, and other anticoagulant drugs may increase risk. (5.5)
- *Activation of Mania/Hypomania*: Screen patients for bipolar disorder. (5.6)
- *Seizures*: Use with caution in patients with seizure disorders. (5.8)
- *Angle-Closure Glaucoma:* Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles, treated with antidepressants (5.9)
- *Sexual Dysfunction:* Paroxetine HCL CR may cause symptoms of sexual dysfunction. (5.13)

## ADVERSE REACTIONS

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

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

**DRUG INTERACTIONS**

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

**USE IN SPECIFIC POPULATIONS**

- *Pregnancy:* SSRI use, particularly later in pregnancy, may increase the risk of persistent pulmonary hypertension and symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, irritability) in the neonate. (5.4, 8.1)
- *Nursing Mothers*: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 9/2023**

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**FULL PRESCRIBING INFORMATION: CONTENTS***

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

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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)].* Paroxetine HCL CR is not approved for use in pediatric patients *[see Use in Specific Populations (8.4)].***

## 1 INDICATIONS AND USAGE

Paroxetine HCL CR is indicated in adults for the treatment of:
- Major depressive disorder (MDD)
- Panic disorder (PD)
- Social anxiety disorder (SAD)
- Premenstrual dysphoric disorder (PMDD)

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Instructions

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

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

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

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

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

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

### 2.3 Dosage in Patients with Premenstrual Dysphoric Disorder

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

In patients with an inadequate response, the dosage may be increased to the maximum

recommended dosage of 25 mg per day, depending on tolerability. Institute dosage adjustments at intervals of at least 1 week.

### 2.4 Screen for Bipolar Disorder Prior to Starting Paroxetine HCL CR

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

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

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

### 2.6 Switching Patients to or from a Monoamine Oxidase Inhibitor Antidepressant

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

### 2.7 Discontinuation of Treatment with Paroxetine HCL CR

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

## 3 DOSAGE FORMS AND STRENGTHS

Paroxetine HCL CR extended-release tablets, USP are available as:

• 12.5 mg yellow, round tablets, one face is plain and the other face is engraved with “12.5”.

• 25 mg pink, round tablets, one face is plain and the other face is engraved with “25”.

• 37.5 mg blue, round tablets, one face is plain and the other face is engraved with “37.5”.

## 4 CONTRAINDICATIONS

Paroxetine HCL CR is contraindicated in patients:

- Taking, or within 14 days of stopping, MAOIs (including the MAOIs linezolid and intravenous methylene blue) because of an increased risk of serotonin syndrome *[See Warnings and Precautions (5.2), Drug Interactions (7)].*
- Paroxetine HCL CR should not be used in patients receiving medications that can prolong QT interval and are also metabolized by CYP450 2D6,such as thioridazine or pimozide [see Drug Interactions (7),Warnings and Precautions (5.3)].
- With known hypersensitivity (e.g., anaphylaxis, angioedema, Stevens-Johnson syndrome) to paroxetine or to any of the inactive ingredients in Paroxetine HCL CR *[see Adverse Reactions (6.1, 6.2)].*

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

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

drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are provided in Table 2.

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

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

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

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

### 5.2 Serotonin Syndrome

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs, including Paroxetine HCL CR, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, 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 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 Paroxetine HCL CR with MAOIs is contraindicated. In addition, do not initiate Paroxetine HCL CR in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Paroxetine HCL CR, discontinue Paroxetine HCL CR before initiating treatment with the MAOI [see *Contraindications* (4), *Drug Interactions*(7.1)].

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

### 5.3 Drug Interactions Leading to QT Prolongation

Cases of QT interval prolongation have been reported, although causality with

Paroxetine HCL CR has not been established.

Paroxetine HCL CR should be used with caution in patients with a history of QT interval prolongation, patients taking anti-arrhythmic or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease.

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 Paroxetine HCL CR is contraindicated in combination with thioridazine and pimozide *[see Contraindications (4), Drug Interactions (7), Clinical Pharmacology (12.3)].*

### 5.4 Embryofetal Toxicity

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, Paroxetine HCL CR 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 Paroxetine HCL CR, increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), other antiplatelet drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. 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 Paroxetine HCL CR and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio.

### 5.6 Activation of Mania or Hypomania

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

### 5.7 Discontinuation Syndrome

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

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

### 5.8 Seizures

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

### 5.9 Angle-Closure Glaucoma

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

### 5.10 Hyponatremia

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

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

### 5.11 Reduction of Efficacy of Tamoxifen

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

### 5.12 Bone Fracture

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

### 5.13 Sexual Dysfunction

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

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

## 6 ADVERSE REACTIONS

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

- Hypersensitivity reactions to paroxetine [see *Contraindications* (4)]
- Suicidal Thoughts and Behaviors [see *Warnings and Precautions* (5.1)]
- Serotonin Syndrome [see *Warnings and Precautions* (5.2)]
- Embryofetal and Neonatal Toxicity [see *Warnings and Precautions* (5.4)]
- Increased Risk of Bleeding [see *Warnings and Precautions* (5.5)]
- Activation of Mania/Hypomania [see *Warnings and Precautions* (5.6)]
- Discontinuation Syndrome [see *Warnings and Precautions* (5.7)]
- Seizures [see *Warnings and Precautions* (5.8)]

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

**6.1 Clinical Trials Experience**

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

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

- Studies 1 and 2 were 12-week studies that enrolled patients 18 to 65 years old who received Paroxetine HCL CR at doses ranging from 25 mg to 62.5 mg once daily. Study 3 was a 12-week study in patients 60 to 88 years old who received Paroxetine HCL CR at doses ranging from 12.5 mg to 50 mg once daily.
- Studies 4, 5, and 6 were 10-week studies in patients 19 to 72 years old who received Paroxetine HCL CR at doses ranging from 12.5 mg to 75 mg once daily.
- Study 7 was a 12-week study that enrolled adult patients who received Paroxetine HCL CR at doses ranging from 12.5 mg to 37.5 mg once daily.
- Studies 8, 9, and 10 were 12-week, placebo-controlled trials in female patients 18 to 46 years old who received Paroxetine HCL CR at doses of 12.5 mg or 25 mg once daily. Study 11 was a 12-week placebo-controlled trial in patients 18 to 46 years old who received Paroxetine HCL CR 2 weeks prior to the onset of menses (luteal phase dosing) at doses of 12.5 mg or 25 mg once daily.

Adverse Reactions Leading to Discontinuation in Patients with MDD, PD, SAD, and PMDD

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

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

Adverse Reactions in MDD, PD, and SAD

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

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

| | **MDD 18 to 65 year olds** | | **MDD ≥60 years old** | | **Panic Disorder** | | **Social Anxiety Disorder** | |
|---|---|---|---|---|---|---|---|---|
| Body System/ Adverse Reaction | Paroxetine HCL CR (N=212) % | Placebo (N=211) % | Paroxetine HCL CR (N=104) % | Placebo (N=109) % | Paroxetine HCL CR (N=444) % | Placebo (N=445) % | Paroxetine HCL CR (N=186) % | Placebo (N=184) % |
| **Body as a Whole** | | | | | | | | |
| Headache | 27 | 20 | 17 | 13 | NA | NA | 23 | 17 |
| Asthenia | 14 | 9 | 15 | 14 | 15 | 10 | 18 | 7 |
| Abdominal Pain | 7 | 4 | - | - | 6 | 4 | 5 | 4 |
| Back Pain | 5 | 3 | - | - | NA | NA | 4 | 1 |
| **Digestive** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **System** | | | | | | | | |
| Nausea | 22 | 10 | - | - | 23 | 17 | 22 | 6 |
| Diarrhea | 18 | 7 | 15 | 9 | 12 | 9 | 9 | 8 |
| Dry Mouth | 15 | 8 | 18 | 7 | 13 | 9 | 3 | 2 |
| Constipation | 10 | 4 | 13 | 5 | 9 | 6 | 5 | 2 |
| Flatulence | 6 | 4 | - | - | NA | NA | NA | NA |
| Decreased Appetite | 4 | 2 | 12 | 5 | 8 | 6 | 1 | <1 |
| Dyspepsia | NA | NA | 13 | 10 | NA | NA | 2 | <1 |
| **Musculoskeletal System** | | | | | | | | |
| Myalgia | NA | NA | - | - | 5 | 3 | NA | NA |
| **Nervous System** | | | | | | | | |
| Somnolence | 22 | 8 | 21 | 12 | 20 | 9 | 9 | 4 |
| Insomnia | 17 | 9 | 10 | 8 | 20 | 11 | 9 | 4 |
| Dizziness | 14 | 4 | 9 | 5 | NA | NA | 7 | 4 |
| Libido Decreased | 7 | 3 | 8 | <1 | 9 | 4 | 8 | 1 |
| Nervousness | NA | NA | - | - | 8 | 7 | NA | NA |
| Tremor | 7 | 1 | 7 | 0 | 8 | 2 | 4 | 2 |
| Anxiety | NA | NA | - | - | 5 | 4 | 2 | 1 |
| **Respiratory System** | | | | | | | | |
| Sinusitis | NA | NA | - | - | 8 | 5 | NA | NA |
| Yawn | 5 | 0 | - | - | 3 | 0 | 2 | 0 |
| **Skin and Appendages** | | | | | | | | |
| Sweating | 6 | 2 | 10 | <1 | 7 | 2 | 14 | 3 |
| **Special Senses** | | | | | | | | |
| Abnormal Vision[a] | 5 | 1 | - | - | 3 | <1 | 2 | 0 |
| **Urogenital System** | | | | | | | | |
| Abnormal Ejaculation[b,c] | 26 | 1 | 17 | 3 | 27 | 3 | 15 | 1 |
| Female Genital Disorder[b,d] | 10 | <1 | - | - | 7 | 1 | 3 | 0 |
| Impotence[b] | 5 | 3 | 9 | 3 | 10 | 1 | 9 | 0 |

Hyphen = the reaction listed occurred in <5% of patients treated with Paroxetine HCL CR

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

[a] Mostly blurred vision

[b] Based on the number of males or females

[c] Mostly anorgasmia or delayed ejaculation

[d] Mostly anorgasmia or delayed orgasm

Other Adverse Reactions Observed During the Premarketing Evaluation of Paroxetine HCL CR

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

Adverse Reactions in Patients with PMDD

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

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

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

NA= the adverse reaction information is not available in this population.

[a] <1% means greater than zero and less than 1%.

[b] The luteal phase and continuous dosing PMDD trials were not designed for making direct comparisons between the 2 dosing regimens.

[c] Mostly anorgasmia or difficulty achieving orgasm.

Dose Dependent Adverse Reactions

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

Male and Female Sexual Dysfunction

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

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

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

| | | Studies 4, 5 and 6 | | Studies 8, 9 and | Study 10 (Luteal |
|---|---|---|---|---|---|

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

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

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

Less Common Adverse Reactions

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

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

*Cardiovascular System*: Infrequent was postural hypotension.

*Hemic and Lymphatic System:* Rare was thrombocytopenia.

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

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

*Psychiatric:* Infrequent were hallucinations.

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

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

### 6.2 Postmarketing Experience

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

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

## 7 DRUG INTERACTIONS

### 7.1 Clinically Significant Drug Interactions with Paroxetine HCL CR

Table 6 includes clinically significant drug interactions with Paroxetine HCL CR.

**Table 6: Clinically Significant Drug Interactions with Paroxetine HCL CR**

| | |
|---|---|
| **Monoamine Oxidase Inhibitors (MAOIs)** | |
| *Clinical Impact* | The concomitant use of SSRIs, including Paroxetine HCL CR, and MAOIs increases the risk of serotonin syndrome. |
| *Intervention* | Paroxetine HCL CR is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue [see *Dosage and Administration* (2.6), *Contraindications* (4), *Warnings and Precautions* (5.2)]. |
| *Examples* | selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue |
| **Pimozide and Thioridazine** | |
| *Clinical Impact* | Paroxetine HCL CR should not be used in patients receiving medications that can prolong QT interval and are metabolized by CYP450 2D6 such as thioridazine or pimozide (see Contraindications and Warnings and Precautions) |
| *Intervention* | Paroxetine HCL CR is contraindicated in patients taking pimozide or thioridazine [see *Contraindications* (4)]. |
| **Other Serotonergic Drugs** | |
| *Clinical Impact* | The concomitant use of serotonergic drugs with Paroxetine HCL CR increases the risk of serotonin syndrome. |
| *Intervention* | Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of Paroxetine HCL CR and/or concomitant serotonergic drugs [see *Warnings and Precautions* (5.2)]. |
| *Examples* | Other SSRIs, SNRIs, triptans, tricyclic antidepressants, opioids, lithium, 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 Paroxetine HCL CR may potentiate the risk of bleeding. |
| *Intervention* | Inform patients of the increased risk of bleeding associated with the concomitant use of Paroxetine HCL CR and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio [see *Warnings and Precautions* (5.5)]. |
| *Examples* | aspirin, clopidogrel, heparin, warfarin |
| **Drugs Highly Bound to Plasma Protein** | |
| *Clinical Impact* | Paroxetine HCL CR is highly bound to plasma protein. The concomitant use of Paroxetine HCL CR with another drug that is highly bound to plasma protein may increase free concentrations of Paroxetine HCL CR or other tightly-bound drugs in plasma. |
| *Intervention* | Monitor for adverse reactions and reduce dosage of Paroxetine HCL CR or other protein-bound drugs as warranted. |
| *Examples* | warfarin |
| **Drugs Metabolized by CYP2D6** | |
| *Clinical Impact* | Paroxetine HCL CR is a CYP2D6 inhibitor [see *Clinical Pharmacology* (12.3)]. The concomitant use of Paroxetine HCL CR with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. |
| *Intervention* | Decrease the dosage of a CYP2D6 substrate if needed with concomitant Paroxetine HCL CR use. Conversely, an increase in dosage of a CYP2D6 substrate may be needed if Paroxetine HCL CR is discontinued. |
| *Examples* | propafenone, flecainide, atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine, risperidone. |
| **Tamoxifen** | |
| *Clinical Impact* | Concomitant use of tamoxifen with Paroxetine HCL CR may lead to reduced plasma concentrations of the active metabolite (endoxifen) and reduced efficacy of tamoxifen |
| *Intervention* | Consider use of an alternative antidepressant little or no CYP2D6 inhibition [see *Warnings and Precautions* (5.11)]. |
| **Fosamprenavir/Ritonavir** | |

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy 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 athttps://womensmentalhealth.org/clinical-and-researchprograms/pregnancy registry/antidepressants/.

Risk Summary

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].*

Paroxetine HCL CR 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 paroxetine use and cardiovascular malformations have reported inconsistent findings, some meta-analyses of epidemiological studies have identified an increased risk of cardiovascular malformations (see Data). There are risks of persistent pulmonary hypertension of the newborn (PPHN) (see Data) and/or poor neonatal adaptation with exposure to selective serotonin reuptake inhibitors (SSRIs), including Paroxetine HCL CR, during pregnancy. There also are risks associated with untreated depression in pregnancy (see Clinical Considerations). For women who intend to become pregnant or who are in their first trimester of pregnancy, paroxetine should be initiated only after consideration of the other available treatment options.

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 are approximately 6 (rat) and less than 2 (rabbit) times the maximum recommended human dose (MRHD -75 mg) on an mg/$m^2$ 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/$m^2$ basis (see Data).

The estimated background risks of major birth defects and miscarriage for the indicated populations 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 major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Maternal Adverse Reactions

Use of Paroxetine HCL CR 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 exposed to Paroxetine HCL CR 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. It should be noted that, in some cases, the clinical picture is 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 to 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 to 4.97). Important limitations of the 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 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality.

Animal Data

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 6 (rat) and less than 2 (rabbit) times the maximum recommended human dose (MRHD – 75 mg) on an mg/m$^2$ basis. These studies have revealed no evidence of malformations. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day 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.

### 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 effects of paroxetine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Paroxetine HCL CR and any potential adverse effects on the breastfed infant from Paroxetine HCL CR or the underlying maternal condition.

Clinical Considerations

Infants exposed to Paroxetine HCL CR 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 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 Paroxetine HCL CR in pediatric patients have not been established [see *Boxed Warning, Warnings and Precautions* (*5.1*)].

Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with immediate-release paroxetine, and effectiveness was not established in pediatric patients. Decreased appetite and weight loss have been observed in association with the use of SSRIs.

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

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

### 8.5 Geriatric Use

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

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

### 8.6 Renal and/or Hepatic Impairment

Increased plasma concentrations of paroxetine occur in patients with renal and hepatic impairment. The initial dosage of Paroxetine HCL CR, should be reduced in patients with severe renal impairment and patients with severe hepatic impairment *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

## 10 OVERDOSAGE

The following have been reported with paroxetine tablet overdosage:

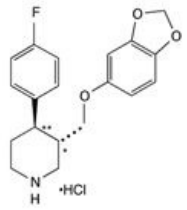
- Seizures, which may be delayed, and altered mental status including coma.
- Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.
- Serotonin syndrome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

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

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

## 11 DESCRIPTION

Paroxetine HCL CR USP, contains paroxetine hydrochloride, an SSRI. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(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 g/mol (329.4 g/mol as free base). The structural formula of paroxetine hydrochloride is:



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

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

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

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

### 12.3 Pharmacokinetics

Absorption

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

Paroxetine extended-release tablets are completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single oral doses of Paroxetine HCL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine $C_{max}$ and $AUC_{0\text{-}inf}$ increased disproportionately with dose (as seen also with immediate-release formulations). Mean $C_{max}$ and $AUC_{0\text{-}inf}$ values at these doses were 2, 5.5, 9, and 12.5 ng/mL, and 121, 261, 338, and 540 ng·hr. /mL, respectively. $T_{max}$ was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The bioavailability of 25 mg Paroxetine HCL CR is not affected by food.

Distribution

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

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would

normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Elimination

*Metabolism*

The mean elimination half-life of paroxetine was 15 to 20 hours throughout a range of single doses of Paroxetine HCL CR (12.5 mg, 25 mg, 37.5 mg, and 50 mg). During repeated administration of Paroxetine HCL CR (25 mg once daily), steady state was reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat-dose study in which normal male and female subjects (n = 23) received Paroxetine HCL CR (25 mg daily), mean steady state $C_{max}$, $C_{min}$, and $AUC_{0-24}$ values were 30 ng/mL, 20 ng/mL, and 550 ng·hr./mL, respectively.

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

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

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

*Excretion*

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

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

Drug Interaction Studies

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

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

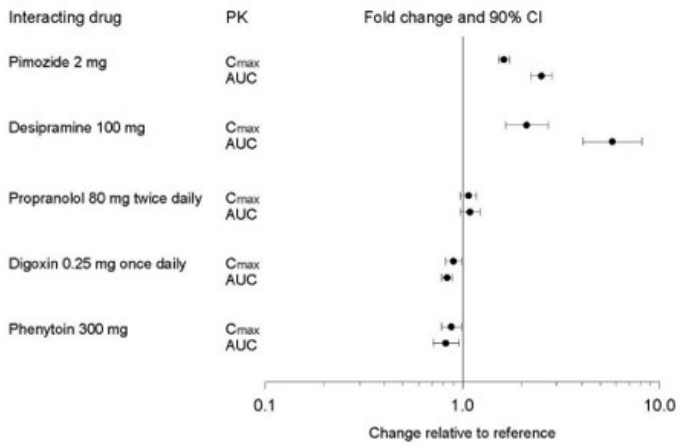
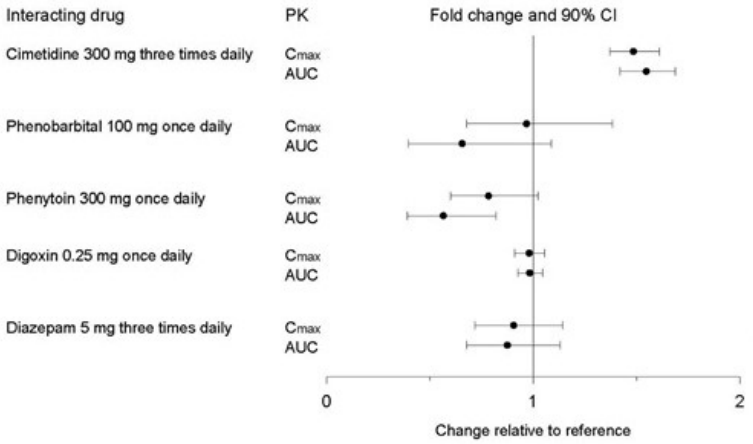



**Figure 2. Impact of Co-Administered Drugs on the Pharmacokinetics of Paroxetine**




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

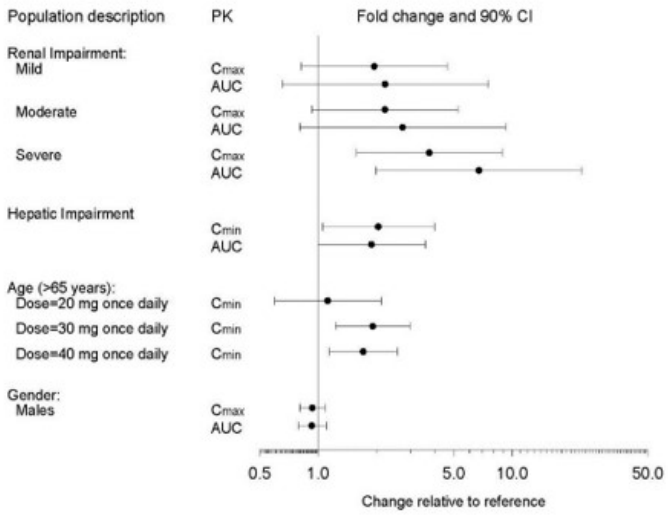
*Drugs Metabolized by Cytochrome CYP3A4*

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

Specific Populations

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

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




## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 1.6 (mouse) and 2.5 (rat) times the MRHD on an mg/m$^2$ basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

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

Impairment of Fertility

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

## 14 CLINICAL STUDIES

### 14.1 Major Depressive Disorder

The efficacy of Paroxetine HCL CR as a treatment for major depressive disorder (MDD) was established in two 12-week, multicenter, randomized, double-blind, placebo-controlled, flexible dose studies with Paroxetine HCL CR (Study 1 and Study 2) in adult patients who met Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for MDD. Study 1 and 2 included patients 18 to 65 years old who received Paroxetine HCL CR doses of 25 to 62.5 mg/day (N= 212) or placebo (N= 211) once daily compared to immediate-release paroxetine 20 to 50 mg (N=217). A third 12-week, multicenter, randomized, double-blind, placebo-controlled, flexible dose study with Paroxetine HCL CR (Study 3) included elderly patients, ranging in age from 60 to 88

years old and used Paroxetine HCL CR doses of 12.5 to 50 mg/day (N=104 ) or placebo (N=109) once daily compared to immediate-release paroxetine 10 to 40 mg (N=106). In all three studies, Paroxetine HCL CR was statistically superior to placebo in improving depressive symptoms as measured by the following: the mean change from baseline in the Hamilton Depression Rating Scale (HDRS) total score at Week 12, the mean change from baseline in the Hamilton Depressed Mood item score at Week 12, and the mean change from baseline in the Clinical Global Impression (CGI)–Severity of Illness score.

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

### 14.2 Panic Disorder

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

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

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

### 14.3 Social Anxiety Disorder

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

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

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

### 14.4 Premenstrual Dysphoric Disorder

The effectiveness of Paroxetine HCL CR for the treatment of Premenstrual Dysphoric

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

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

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

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Paroxetine HCL CR extended-release tablets, USP are available as:

12.5 mg yellow, round tablets, one face is plain and the other face is engraved with “12.5”.

Bottles of 30 NDC 60505-1316-3

25 mg pink, round tablets, one face is plain and the other face is engraved with “25”.

Bottles of 30 NDC 60505-1317-3

37.5 mg blue, round tablets, one face is plain and the other face is engraved with “37.5”.

Bottles of 30 NDC 60505-1318-3

Store at or below 25°C (77°F); [see USP].

## 17 PATIENT COUNSELING INFORMATION

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

Suicidal Thoughts and Behaviors

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

Important Administration Instructions

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

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of Paroxetine HCL CR with other serotonergic drugs including triptans, tricyclic antidepressants, opioids, lithium, tryptophan, buspirone, amphetamines, St. John’s Wort, and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid). Instruct patients to contact their 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* (7.1)].

Concomitant Medications

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

Increased Risk of Bleeding

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

Activation of Mania/Hypomania

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

Discontinuation Syndrome

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

Sexual Dysfunction

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

Embryo-Fetal Toxicity

Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with Paroxetine HCL CR. Advise women of risks associated with first trimester use of Paroxetine HCL CR and that use later in pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN) [see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]. Advise women that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Paroxetine HCL CR during pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (8.1)].

Lactation

Advise breastfeeding women using Paroxetine HCL CR 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)].

Females and Males of Reproductive Potential

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

Allergic Reactions

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

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